An analysis of cumulative risks based on biomonitoring data for six phthalates using the Maximum Cumulative Ratio

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ABSTRACT

Background: The Maximum Cumulative Ratio (MCR) quantifies the degree to which a single chemical drives the cumulative risk of an individual exposed to multiple chemicals. Phthalates are a class of chemicals with ubiquitous exposures in the general population.

Objectives: To use the MCR to evaluate coexposures to six phthalates as measured in biomonitoring data from most recent cycle of the National Health and Nutrition Examination Survey (NHANES).

Methods: The values of MCR, Hazard Index (HI), and phthalate-specific Hazard Quotients (HQs) were determined for NHANES participants by calculating steady-state doses consistent with concentrations of metabolites in urine and using Tolerable Daily Intake values.

Results: There were 21 participants (0.8% of the NHANES sample) with $HI > 1$. Of those, 43% (9/21) would be missed by chemical-by-chemical assessments (i.e. all HQs were less than or equal to one). The median MCR value was 2.0 and HI and MCR values were negatively correlated ($p < 0.001$) indicating that most participants, especially those with elevated HI values, had their cumulative risks driven by relatively large doses of a single phthalate rather than doses of multiple phthalates. The probability of having $HI > 1$ was not driven by age, gender, or ethnicity. Cumulative exposures of concern originated from three of the fifteen possible pairs of the six phthalates.

Conclusion: These findings suggest that cumulative exposures were a potential concern for a small portion of the surveyed participants involving a subset of the phthalates explored. However, the largest risks were dominated by exposures to a single phthalate.

INTRODUCTION

Phthalates (esters of phthalic acid) are used as plasticizers in a wide range of consumer goods including vinyl flooring, food packaging, the outer coatings of pills, cosmetics, food containers, pipes and tubing, etc. [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.17226/12528", "ISBN" : "9780309128421 0309128420", "abstract" : "People are exposed to a variety of chemicals throughout their daily lives. To protect public health, regulators use risk assessments to examine the effects of chemical exposures. This book provides guidance for assessing the risk of phthalates, chemicals found in many consumer products that have been shown to affect the development of the male reproductive system of laboratory animals. Because people are exposed to multiple phthalates and other chemicals that affect male reproductive development, a cumulative risk assessment should be conducted that evaluates the combined effects of exposure to all these chemicals. The book suggests an approach for cumulative risk assessment that can serve as a model for evaluating the health risks of other types of chemicals.", "author" : [{ "dropping-particle" : "", "family" : "NRC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-1", "issued" : { "date-parts" : [["2008"]] }, "number-of-pages" : "208", "publisher" : "Committee on the Health Risks of Phthalates, National Research Council", "publisher-place" : "Washington, DC", "title" : "Phthalates and Cumulative Risk Assessment: The Task Ahead", "type" : "book" }, "uris" : ["http://www.mendeley.com/documents/?uuid=26d90756-8dff-4b5d-9265-cb536d575511"] }], "mendeley" : { "formattedCitation" : "(NRC 2008)", "plainTextFormattedCitation" : "(NRC 2008)", "previouslyFormattedCitation" : "(NRC 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. As plasticizers, phthalates can make nail polish less brittle, allow hair sprays to have more flexibility, and reduce the volatility in fragrances. Phthalates are not strongly bound and leaching of the compounds can occur in many of these products [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "doi.org/10.1016/j.cppeds.2007.11.001", "author" : [{ "dropping-particle" : "", "family" : "Sathyanarayana", "given" : "Sheela", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Current Problems in Pediatric and Adolescent Health Care", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2008"]] }, "page" : "34-49", "title" : "Phthalates and Children\u2019s Health", "type" : "article-journal", "volume" : "38" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0bf47f51-307f-4f53-b667-be4526a06fdf"] }], "mendeley" : { "formattedCitation" : "(Sathyanarayana 2008)", "plainTextFormattedCitation" : "(Sathyanarayana 2008)", "previouslyFormattedCitation" : "(Sathyanarayana 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Human exposure routes include dermal exposures, inhalation, and, most commonly, ingestion [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1289/ehp.0901712", "ISBN" : "1552-9924 (Electronic)\\r0091-6765 (Linking)", "ISSN" : "15529924", "PMID" : "20392686", "abstract" : "BACKGROUND: Phthalates are compounds that are used in a wide range of consumer products. However, the contribution of dietary intake to phthalate exposure has not been well defined. OBJECTIVE: The objective of this study was to assess the contribution of different food types to phthalate exposure. Phthalates are chemicals of concern because of the high levels measured in people and the environment, as well as the demonstrated toxicity in animal studies and limited epidemiological studies. Previous research, although limited, has suggested that phthalates contaminate food in various countries. METHODS: We conducted an exploratory analysis of data collected as part of the 2003-2004 National Health and Nutrition Examination Survey (NHANES). Associations between dietary intake (assessed by a 24-hr dietary recall) for a range of food types (meat, poultry, fish, fruit, vegetable, and dairy) and phthalate metabolites measured in urine were analyzed using multiple linear regression modeling. RESULTS: We found that metabolites of di-(2-ethylhexyl)

phthalate (DEHP) and high-molecular-weight phthalate metabolites were associated with the consumption of poultry. Monoethyl phthalate, the metabolite of diethyl phthalate (DEP), was associated with vegetable consumption, specifically tomato and potato consumption. DISCUSSION: These results, combined with results from previous studies, suggest that diet is an important route of intake for phthalates. Further research is needed to determine the sources of food contamination with these toxic chemicals and to describe the levels of contamination of U.S. food in a large, representative U.S. sample.", "author" : [{ "dropping-particle" : "", "family" : "Colacino", "given" : "Justin A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "T. Robert", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schecter", "given" : "Arnold", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-1", "issue" : "7", "issued" : { "date-parts" : [["2010"]] }, "page" : "998-1003", "title" : "Dietary intake is associated with phthalate body burden in a nationally representative sample", "type" : "article-journal", "volume" : "118" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d1943532-6754-4168-8969-3e877f169a27"] }], "mendeley" : { "formattedCitation" : "(Colacino et al. 2010)", "plainTextFormattedCitation" : "(Colacino et al. 2010)", "previouslyFormattedCitation" : "(Colacino et al. 2010)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. In 2008, the National Research Council concluded that phthalates met the conditions to warrant a cumulative risk approach. They stated that the general population is exposed to multiple phthalates which may contribute to a common adverse health outcomes [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.17226/12528", "ISBN" : "9780309128421 0309128420", "abstract" : "People are exposed to a variety of chemicals throughout their daily lives. To protect public health, regulators use risk assessments to examine the effects of chemical exposures. This book provides guidance for assessing the risk of phthalates, chemicals found in many consumer products that have been shown to affect the development of the male reproductive system of laboratory animals. Because people are exposed to multiple phthalates and other chemicals that affect male reproductive development, a cumulative risk assessment should be conducted that evaluates the combined effects of exposure to all these chemicals. The book suggests an approach for cumulative risk assessment that can serve as a model for evaluating the health risks of other types of chemicals.", "author" : [{ "dropping-particle" : "", "family" : "NRC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-1", "issued" : { "date-parts" : [["2008"]] }, "number-of-pages" : "208", "publisher" : "Committee on the Health Risks of Phthalates, National Research Council", "publisher-place" : "Washington, DC", "title" : "Phthalates and Cumulative Risk Assessment: The Task Ahead", "type" : "book" }, "uris" : ["http://www.mendeley.com/documents/?uuid=26d90756-8dff-4b5d-9265-cb536d575511"] }], "mendeley" : { "formattedCitation" : "(NRC 2008)", "plainTextFormattedCitation" : "(NRC 2008)", "previouslyFormattedCitation" : "(NRC 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Although the NRC report focused on effects related to disrupted male reproductive development known as the “phthalate syndrome”, there is evidence from both animal and human studies that phthalates impact a wide variety of health endpoints (see recent reviews including: [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.2478/s13382-011-0022-2", "author" : [{ "dropping-particle" : "", "family" : "Jurewicz", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hanke", "given" : "W", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Occupational Medicine and Environmental Health", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2011"]] }, "page" : "115-141", "title" : "Exposure to phthalates: Reproductive outcome and children health. A review of epidemiological studies", "type" : "article-journal", "volume" : "24" }, "uris" : [

"http://www.mendeley.com/documents/?uuid=fe322fcd-d0fc-4335-9525-bf6dd93a70c1"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1080/10937400903094091", "ISSN" : "1521-6950", "PMID" : "20183522", "abstract" : "The purposes of this review are to (1) evaluate human and experimental evidence for adverse effects on reproduction and development in humans, produced by exposure to phthalates, and (2) identify knowledge gaps as for future studies. The widespread use of phthalates in consumer products leads to ubiquitous and constant exposure of humans to these chemicals. Phthalates were postulated to produce endocrine-disrupting effects in rodents, where fetal exposure to these compounds was found to induce developmental and reproductive toxicity. The adverse effects observed in rodent models raised concerns as to whether exposure to phthalates represents a potential health risk to humans. At present, di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), and butyl benzyl phthalate (BBP) have been demonstrated to produce reproductive and developmental toxicity; thus, this review focuses on these chemicals. For the general population, DEHP exposure is predominantly via food. The average concentrations of phthalates are highest in children and decrease with age. At present, DEHP exposures in the general population appear to be close to the tolerable daily intake (TDI), suggesting that at least some individuals exceed the TDI. In addition, specific high-risk groups exist with internal levels that are several orders of magnitude above average. Urinary metabolites used as biomarkers for the internal levels provide additional means to determine more specifically phthalate exposure levels in both general and high-risk populations. However, exposure data are not consistent and there are indications that secondary metabolites may be more accurate indicators of the internal exposure compared to primary metabolites. The present human toxicity data are not sufficient for evaluating the occurrence of reproductive effects following phthalate exposure in humans, based on existing relevant animal data. This is especially the case for data on female reproductive toxicity, which are scarce. Therefore, future research needs to focus on developmental and reproductive endpoints in humans. It should be noted that phthalates occur in mixtures but most toxicological information is based on single compounds. Thus, it is concluded that it is important to improve the knowledge of toxic interactions among the different chemicals and to develop measures for combined exposure to various groups of phthalates.", "author" : [{ "dropping-particle" : "", "family" : "Lyche", "given" : "Jan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gutleb", "given" : "Arno C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bergman", "given" : "Ake", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Eriksen", "given" : "Gunnar S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murk", "given" : "AlberTinka J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ropstad", "given" : "Erik", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saunders", "given" : "Margaret", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Skaare", "given" : "Janneche U", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of toxicology and environmental health. Part B, Critical reviews", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2009"]] }, "page" : "225-249", "title" : "Reproductive and developmental toxicity of phthalates.", "type" : "article-journal", "volume" : "12" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9175a436-bf8e-41a2-aab4-4297d0c854ad"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1002/mnfr.200800312", "author" : [{ "dropping-particle" : "", "family" : "Martino-Andrade", "given" : "Anderson Joel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chahoud", "given" : "Ibrahim", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular Nutrition & Food Research", "id" : "ITEM-3", "issue" : "1", "issued" : { "date-parts" : [["2009"]] }, "page" : "148-157", "title" : "Reproductive toxicity of phthalate esters", "type" : "article-journal", "volume" : "54" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cd2a6776-4d0e-40df-b41d-676001dcef2e"] }, { "id" :

"ITEM-4", "itemData" : { "DOI" : "10.1289/ehp.1103582", "ISBN" : "0091-6765", "ISSN" : "00916765", "PMID" : "21749963", "abstract" : "BACKGROUND: Limited animal, in vitro, and human studies have reported that exposure to phthalates or bisphenol A (BPA) may affect thyroid signaling.\\n\\nOBJECTIVE: We explored the cross-sectional relationship between urinary concentrations of metabolites of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and BPA with a panel of serum thyroid measures among a representative sample of U.S. adults and adolescents.\\n\\nMETHODS: We analyzed data on urinary biomarkers of exposure to phthalates and BPA, serum thyroid measures, and important covariates from 1,346 adults (ages \u2265 20 years) and 329 adolescents (ages 12-19 years) from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 using multivariable linear regression.\\n\\nRESULTS: Among adults, we observed significant inverse relationships between urinary DEHP metabolites and total thyroxine (T4), free T4, total triiodothyronine (T3), and thyroglobulin, and positive relationships with thyroid-stimulating hormone (TSH). The strongest and most consistent relationships involved total T4, where adjusted regression coefficients for quintiles of oxidative DEHP metabolites displayed monotonic dose-dependent decreases in total T4 (p-value for trend < 0.0001). Suggestive inverse relationships between urinary BPA and total T4 and TSH were also observed. Conversely, among adolescents, we observed significant positive relationships between DEHP metabolites and total T3. Mono(3-carboxypropyl) phthalate, a secondary metabolite of both DBP and di-n-octyl phthalate, was associated with several thyroid measures in both age groups, whereas other DBP metabolites were not associated with thyroid measures.\\n\\nCONCLUSIONS: These results support previous reports of associations between phthalates-and possibly BPA--and altered thyroid hormones. More detailed studies are needed to determine the temporal relationships and potential clinical and public health implications of these associations.", "author" : [{ "dropping-particle" : "", "family" : "Meeker", "given" : "John D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ferguson", "given" : "Kelly K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-4", "issue" : "10", "issued" : { "date-parts" : [["2011"]] }, "page" : "1396-1402", "title" : "Relationship between urinary phthalate and bisphenol a concentrations and serum thyroid measures in u.s. adults and adolescents from the national health and nutrition examination survey (NHANES) 2007-2008", "type" : "article-journal", "volume" : "119" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9e5227c1-df07-4d59-89ba-ed297dc07017"] }, { "id" : "ITEM-5", "itemData" : { "DOI" : "10.1177/216507991105900505", "author" : [{ "dropping-particle" : "", "family" : "Pak", "given" : "Victoria M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "McCauley", "given" : "Linda A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pinto-Martin", "given" : "Jennifer", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "AAOHN J", "id" : "ITEM-5", "issue" : "5", "issued" : { "date-parts" : [["2011"]] }, "page" : "228-235", "title" : "Phthalate Exposures and Human Health Concerns: A Review and Implications for Practice", "type" : "article-journal", "volume" : "59" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cb3a0f01-3581-4ae8-aa21-34f4abbbb9ee"] }], "mendeley" : { "formattedCitation" : "(Jurewicz and Hanke 2011; Lyche et al. 2009; Martino-Andrade and Chahoud 2009; Meeker and Ferguson 2011; Pak et al. 2011)", "manualFormatting" : "Jurewicz and Hanke 2011; Lyche et al. 2009; Martino-Andrade and Chahoud 2009; Meeker and Ferguson 2011; Pak et al. 2011", "plainTextFormattedCitation" : "(Jurewicz and Hanke 2011; Lyche et al. 2009; Martino-Andrade and Chahoud 2009; Meeker and Ferguson 2011; Pak et al. 2011)", "previouslyFormattedCitation" : "(Jurewicz and Hanke 2011; Lyche et al. 2009; Martino-Andrade and Chahoud 2009; Meeker and Ferguson 2011; Pak et al. 2011)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]).

The Hazard Index (HI) is a screening tool for estimating cumulative risks from exposures to multiple chemicals from a common mechanism group. This approach assumes dose addition [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "EPA/630/P-02/001F", "author" : [{ "dropping-particle" : "", "family" : "EPA", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "EPA guide", "id" : "ITEM-1", "issued" : { "date-parts" : [["2003"]] }, "publisher-place" : "Washington Office, Washington, DC", "title" : "Framework for Cumulative Risk Assessment", "type" : "report" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e0967bd8-cc57-4fd0-aded-0372c6be9fd8"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "EPA/600/R-06/013F", "author" : [{ "dropping-particle" : "", "family" : "EPA", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-2", "issued" : { "date-parts" : [["2007"]] }, "publisher-place" : "Washington, DC", "title" : "Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (Final Report)", "type" : "report" }, "uris" : ["http://www.mendeley.com/documents/?uuid=be96df41-64f7-473f-93f5-f7b357cc307b"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1016/0300-483X(95)03207-V", "ISBN" : "0300-483X (Print)\\r0300-483X (Linking)", "ISSN" : "0300-483X", "PMID" : "8571352", "abstract" : "Humans are typically exposed to low doses of combinations of chemicals rather than to one or two chemicals at a time, yet most of the available toxicity data provide information on single chemicals or binary pairs, rather than on whole mixtures. The use of existing interactions study data for the quantitative risk assessment of chemical mixtures is problematic. These studies generally lack the necessary statistical characterizations to be useful in quantitative risk assessment procedures. The U.S. EPA developed guidelines for risk assessment for chemical mixtures in 1986 and is currently in the process of making revisions. Significant advances have been made in both the theoretical development and application of procedures such as dose addition, response addition, toxicity equivalence factors, comparative potency and interactions data characterizations. Details on the current revisions to the guidelines are given, along with information on the research efforts that have influenced these revisions or that represent future directions in chemical mixtures risk assessment.", "author" : [{ "dropping-particle" : "", "family" : "Teuschler", "given" : "L K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hertzberg", "given" : "R C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Toxicology", "id" : "ITEM-3", "issue" : "2-3", "issued" : { "date-parts" : [["1995"]] }, "page" : "137-144", "title" : "Current and future risk assessment guidelines, policy, and methods development for chemical mixtures.", "type" : "article-journal", "volume" : "105" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c0686d96-e9f2-492b-9620-7f498a4d6df1"] }, { "id" : "ITEM-4", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "EPA", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Risk Assessment Forum", "id" : "ITEM-4", "issue" : "185", "issued" : { "date-parts" : [["1986"]] }, "number-of-pages" : "34014-34025", "publisher-place" : "Washington Office, Washington, DC", "title" : "Guidelines for the Health Risk Assessment of Chemical Mixtures", "type" : "report", "volume" : "51" }, "uris" : ["http://www.mendeley.com/documents/?uuid=be495416-d2be-4d49-8a18-17b69b8ed9e8"] }], "mendeley" : { "formattedCitation" : "(EPA 1986, 2003, 2007; Teuschler and Hertzberg 1995)", "plainTextFormattedCitation" : "(EPA 1986, 2003, 2007; Teuschler and Hertzberg 1995)", "previouslyFormattedCitation" : "(EPA 1986, 2003, 2007; Teuschler and Hertzberg 1995)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. The HI provides a straightforward method for quantifying risks by relating the intake of a group of substances to their Reference Values (RfVs) [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.17226/12528", "ISBN" : "9780309128421 0309128420", "abstract" : "People are exposed to a variety of chemicals throughout their daily lives. To protect public health, regulators use risk assessments to examine the effects of chemical exposures. This book provides

guidance for assessing the risk of phthalates, chemicals found in many consumer products that have been shown to affect the development of the male reproductive system of laboratory animals. Because people are exposed to multiple phthalates and other chemicals that affect male reproductive development, a cumulative risk assessment should be conducted that evaluates the combined effects of exposure to all these chemicals. The book suggests an approach for cumulative risk assessment that can serve as a model for evaluating the health risks of other types of chemicals.", "author" : [{ "dropping-particle" : "", "family" : "NRC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-1", "issued" : { "date-parts" : [["2008"]] }, "number-of-pages" : "208", "publisher" : "Committee on the Health Risks of Phthalates, National Research Council", "publisher-place" : "Washington, DC", "title" : "Phthalates and Cumulative Risk Assessment: The Task Ahead", "type" : "book" }, "uris" : ["http://www.mendeley.com/documents/?uuid=26d90756-8dff-4b5d-9265-cb536d575511"] }], "mendeley" : { "formattedCitation" : "(NRC 2008)", "plainTextFormattedCitation" : "(NRC 2008)", "previouslyFormattedCitation" : "(NRC 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. This technique applied to individuals has been previously demonstrated in the literature [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1111/j.1365-2605.2009.01047.x", "author" : [{ "dropping-particle" : "", "family" : "Kortenkamp", "given" : "Andreas", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Faust", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Andrology", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2010"]] }, "page" : "463-474", "title" : "No TitleCombined exposures to anti-androgenic chemicals: steps towards cumulative risk assessment", "type" : "article-journal", "volume" : "33" }, "uris" : ["http://www.mendeley.com/documents/?uuid=519b5119-ae87-45d4-a700-6f6c370006db"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1111/j.1365-2605.2011.01240.x", "author" : [{ "dropping-particle" : "", "family" : "S\u00f8eborg", "given" : "T.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Frederiksen", "given" : "H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Andersson", "given" : "A. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Andrology", "id" : "ITEM-2", "issue" : "2", "issued" : { "date-parts" : [["2012"]] }, "page" : "245-252", "title" : "Cumulative risk assessment of phthalate exposure of Danish children and adolescents using the hazard index approach", "type" : "article-journal", "volume" : "35" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7276803c-c0fe-4cb4-b389-3db0bcaa7ee9"] }], "mendeley" : { "formattedCitation" : "(Kortenkamp and Faust 2010; S\u00f8eborg et al. 2012)", "plainTextFormattedCitation" : "(Kortenkamp and Faust 2010; S\u00f8eborg et al. 2012)", "previouslyFormattedCitation" : "(Kortenkamp and Faust 2010; S\u00f8eborg et al. 2012)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Examples of RfVs for oral exposures include the United States Environmental Protection Agency's (USEPA's) Reference Dose (RfD) and the European Union's Tolerable Daily Intake (TDI). The Hazard Quotient (HQ) is calculated as the ratio of an individual's estimated exposure level to the RfV for that chemical. The chemical-specific HQs are then summed to give an individual's HI.

The Maximum Cumulative Ratio (MCR) is a measure of the dominance of the single most problematic chemical posed by cumulative exposures to multiple chemicals within an individual by utilizing both the HI and the HQs [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.3390/ijerph8062212", "ISBN" : "1660-4601", "ISSN" : "16604601", "PMID" : "21776227", "abstract" : "Due to the vast number of possible combinations of chemicals to which individuals are exposed and the resource-intensive nature of cumulative risk assessments, there is a need to determine when cumulative assessments are most required. This paper proposes the use of the maximum

cumulative ratio (MCR) as a tool for this evaluation. MCR is the ratio of the cumulative toxicity received by an individual from exposure to multiple chemical stressors to the largest toxicity from a single chemical stressor. The MCR is a quantitative measure of the difference in an individual's toxicity estimated using a chemical-by-chemical approach and using an additive model of toxicity. As such, it provides a conservative estimate of the degree to which individuals' toxicities could be underestimated by not performing a cumulative risk assessment. In an example application, MCR is shown to be applicable to the evaluation of cumulative exposures involving up to 81 compounds and to provide key insights into the cumulative effects posed by exposures to multiple chemicals. In this example, MCR values suggest that individuals exposed to combinations of chemicals with the largest Hazard Indices were dominated by the contributions of one or two compounds.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "Paul S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Environmental Research and Public Health", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2011"]] }, "page" : "2212-2225", "title" : "Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment", "type" : "article-journal", "volume" : "8" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e0ca9bb7-517b-445c-9a10-b9dc1d270fe2"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.2788/84264", "ISBN" : "9789279384790", "author" : [{ "dropping-particle" : "", "family" : "Kienzler", "given" : "Aude", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berggren", "given" : "Elisabet", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bessems", "given" : "Jos", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bopp", "given" : "Stephanie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "Van Der", "family" : "Linden", "given" : "Sander", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Worth", "given" : "Andrew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-2", "issued" : { "date-parts" : [["2014"]] }, "number-of-pages" : "136", "title" : "Assessment of Mixtures - Review of Regulatory Requirements and Guidance", "type" : "report" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b16adb33-1ec8-4e65-9300-498cbe88c956"] }], "mendeley" : { "formattedCitation" : "(Kienzler et al. 2014; Price and Han 2011)", "plainTextFormattedCitation" : "(Kienzler et al. 2014; Price and Han 2011)", "previouslyFormattedCitation" : "(Kienzler et al. 2014; Price and Han 2011)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. The MCR along with measures of cumulative exposures can inform risk management decisions and help identify specific combinations of chemicals that result in elevated cumulative risks. The MCR approach has been applied to biomonitoring data on mixtures of dioxin-like chemicals [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/jes.2012.74", "ISSN" : "1559-064X", "PMID" : "22781437", "abstract" : "Maximum cumulative ratio (MCR) is a person's cumulative exposure to multiple chemicals divided by the maximum chemical-specific exposure where exposure is expressed on a toxicologically equivalent basis. It is a tool for assessing the need for performing cumulative exposure assessments. In this paper, MCR values were calculated for the three groups of individuals with biomonitoring data of 26 dioxin-like compounds (DLCs) based on the World Health Organization toxic equivalent factors (TEFs). Although the two occupational groups have higher total toxicity equivalence (TEQ) levels than the NHANES group, average MCR values of the three groups are similar (3.5, 3.6, and 3.2). These MCR values are higher than those seen in our earlier studies, supporting the practice of performing cumulative assessments for DLCs. The MCR values also indicate that only 2-5 of the 26 chemicals make significant contributions to total TEQ values. Interestingly, MCR is negatively correlated with total TEQ (in all the three groups) and age (in the NHANES group).

Additionally, MCR is lower in workers where occupational exposures are larger than background exposures. Although overall exposure is the first factor to consider in any mixtures assessment, this paper confirms the usefulness of MCR as a tool for analyzing the pattern of chemical-specific contributions to the total exposure levels of mixtures based on biomonitoring data when TEFs or similar approaches are available.", "author" : [{ "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of exposure science & environmental epidemiology", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2013"]] }, "page" : "343-9", "publisher" : "Nature Publishing Group", "title" : "Applying the maximum cumulative ratio methodology to biomonitoring data on dioxin-like compounds in the general public and two occupationally exposed populations", "type" : "article-journal", "volume" : "23" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c1298fe7-b0c5-4454-b2c2-e15baeac76ea"] }], "mendeley" : { "formattedCitation" : "(Han and Price 2013)", "plainTextFormattedCitation" : "(Han and Price 2013)", "previouslyFormattedCitation" : "(Han and Price 2013)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }], exposures to mixtures of chemicals in water [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.3390/ijerph8124729", "ISBN" : "1661-7827", "ISSN" : "16604601", "PMID" : "22408599", "abstract" : "The maximum cumulative ratio (MCR) developed in previous work is a tool to evaluate the need to perform cumulative risk assessments. MCR is the ratio of the cumulative exposures to multiple chemicals to the maximum exposure from one of the chemicals when exposures are described using a common metric. This tool is used to evaluate mixtures of chemicals measured in samples of untreated ground water as source for drinking water systems in the United States. The mixtures of chemicals in this dataset differ from those examined in our previous work both in terms of the predicted toxicity and compounds measured. Despite these differences, MCR values in this study follow patterns similar to those seen earlier. MCR values for the mixtures have a mean (range) of 2.2 (1.03-5.4) that is much smaller than the mean (range) of 16 (5-34) in the mixtures in previous study. The MCR values of the mixtures decline as Hazard Index (HI) values increase. MCR values for mixtures with larger HI values are not affected by possible contributions from chemicals that may occur at levels below the detection limits. This work provides a second example of use of the MCR tool in the evaluation of mixtures that occur in the environment. \u00a9 2011 by the authors; licensee MDPI, Basel, Switzerland.", "author" : [{ "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Environmental Research and Public Health", "id" : "ITEM-1", "issue" : "12", "issued" : { "date-parts" : [["2011"]] }, "page" : "4729-4745", "title" : "Determining the maximum cumulative ratios for mixtures observed in ground water wells used as drinking water supplies in the United States", "type" : "article-journal", "volume" : "8" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7b6721b3-394f-4394-9393-2ef887f5ca4f"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.3390/ijerph8062212", "ISBN" : "1660-4601", "ISSN" : "16604601", "PMID" : "21776227", "abstract" : "Due to the vast number of possible combinations of chemicals to which individuals are exposed and the resource-intensive nature of cumulative risk assessments, there is a need to determine when cumulative assessments are most required. This paper proposes the use of the maximum cumulative ratio (MCR) as a tool for this evaluation. MCR is the ratio of the cumulative toxicity received by an individual from exposure to multiple chemical stressors to the largest toxicity from a single chemical stressor. The MCR is a quantitative measure of the difference in an individual's toxicity estimated using a chemical-by-chemical approach and using an additive model of toxicity. As such, it provides a conservative estimate of the degree to which individuals' toxicities could be underestimated by not performing a cumulative risk assessment. In an example application, MCR is

shown to be applicable to the evaluation of cumulative exposures involving up to 81 compounds and to provide key insights into the cumulative effects posed by exposures to multiple chemicals. In this example, MCR values suggest that individuals exposed to combinations of chemicals with the largest Hazard Indices were dominated by the contributions of one or two compounds.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "Paul S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "International Journal of Environmental Research and Public Health", "id" : "ITEM-2", "issue" : "6", "issued" : { "date-parts" : [["2011"]] }, "page" : "2212-2225", "title" : "Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment", "type" : "article-journal", "volume" : "8" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e0ca9bb7-517b-445c-9a10-b9dc1d270fe2"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1016/j.scitotenv.2014.01.083", "ISBN" : "00489697", "ISSN" : "00489697", "PMID" : "24565859", "abstract" : "The maximum cumulative ratio (MCR) method allows the categorisation of mixtures according to whether the mixture is of concern for toxicity and if so whether this is driven by one substance or multiple substances. The aim of the present study was to explore, by application of the MCR approach, whether health risks due to indoor air pollution are dominated by one substance or are due to concurrent exposure to various substances. Analysis was undertaken on monitoring data of four European indoor studies (giving five datasets), involving 1800 records of indoor air or personal exposure.Application of the MCR methodology requires knowledge of the concentrations of chemicals in a mixture together with health-based reference values for those chemicals. For this evaluation, single substance health-based reference values (RVs) were selected through a structured review process.The MCR analysis found high variability in the proportion of samples of concern for mixture toxicity. The fraction of samples in these groups of concern varied from 2% (Flemish schools) to 77% (EXPOLIS, Basel, indoor), the variation being due not only to the variation in indoor air contaminant levels across the studies but also to other factors such as differences in number and type of substances monitored, analytical performance, and choice of RVs. However, in 4 out of the 5 datasets, a considerable proportion of cases were found where a chemical-by-chemical approach failed to identify the need for the investigation of combined risk assessment.Although the MCR methodology applied in the current study provides no consideration of commonality of endpoints, it provides a tool for discrimination between those mixtures requiring further combined risk assessment and those for which a single-substance assessment is sufficient. ?? 2014 Elsevier B.V.", "author" : [{ "dropping-particle" : "", "family" : "Brouwere", "given" : "Katleen", "non-dropping-particle" : "De", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cornelis", "given" : "Christa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arvanitis", "given" : "Athanasios", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Brown", "given" : "Terry", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Crump", "given" : "Derrick", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harrison", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jantunen", "given" : "Matti", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Torfs", "given" : "Rudi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Science of the Total Environment", "id" : "ITEM-3", "issue" : "1", "issued" : { "date-parts" : [["2014"]] }, "page" : "267-276", "publisher" : "Elsevier B.V.", "title" : "Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air", "type" : "article-journal", "volume" : "479-480" }, "uris" : ["http://www.mendeley.com/documents/?uuid=88b4562e-de8c-4ca9-a413-b89213445bba"] }, { "id" : "ITEM-4", "itemData" : { "DOI" : "10.1007/s11356-014-3857-9", "ISBN" : "1001-0742", "ISSN" :

"16147499", "PMID" : "25424034", "abstract" : "A two-tiered outline for the predictive environmental risk assessment of chemical mixtures with effect assessments based on concentration addition (CA) approaches as first tier and consideration of independent action (IA) as the second tier was applied based on realistic pesticide mixtures measured in surface waters from 2002 to 2008 within three important Portuguese river basins (`Mondego', `Sado' and `Tejo'). The CA-based risk quotients, based on acute data and an assessment factor of 100, exceeded 1 in more than 39\u00a0{%} of the 281 samples, indicating a potential risk for the aquatic environment, namely to algae. Seven herbicide compounds and three insecticides were the most toxic compounds in the pesticide mixtures and provided at least 50\u00a0{%} of the mixture's toxicity in almost 100\u00a0{%} of the samples with risk quotients based on the sum of toxic units (RQSTU) above 1. In eight samples, the maximum cumulative ratio (MCR) and the Junghan's ratio values indicated that a chemical-by-chemical approach underestimated the toxicity of the pesticide mixtures, and CA predicted higher mixture toxicity than that of IA. From a risk management perspective, the results pointed out that, by deriving appropriate programmes of measures to a limited number of pesticides with the highest contribution to the total mixture toxicity, relevant benefits also on mixture impact could be produced.", "author" : [{ "dropping-particle" : "", "family" : "Silva", "given" : "Em\u00edlia", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cerejeira", "given" : "Maria Jos\u00e9", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Science and Pollution Research", "id" : "ITEM-4", "issue" : "9", "issued" : { "date-parts" : [["2015"]] }, "page" : "6756-6765", "title" : "Concentration addition-based approach for aquatic risk assessment of realistic pesticide mixtures in Portuguese river basins", "type" : "article-journal", "volume" : "22" }, "uris" : ["http://www.mendeley.com/documents/?uuid=2e232d1c-57ec-41f3-8396-5a94569702ec"] }, { "id" : "ITEM-5", "itemData" : { "DOI" : "10.1021/acs.est.5b06267", "ISSN" : "0013-936X", "author" : [{ "dropping-particle" : "", "family" : "Vallotton", "given" : "Nathalie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Science & Technology", "id" : "ITEM-5", "issue" : "10", "issued" : { "date-parts" : [["2016"]] }, "page" : "5286-5293", "title" : "Use of the Maximum Cumulative Ratio As an Approach for Prioritizing Aquatic Coexposure to Plant Protection Products: A Case Study of a Large Surface Water Monitoring Database", "type" : "article-journal", "volume" : "50" }, "uris" : ["http://www.mendeley.com/documents/?uuid=27bc6604-14bf-4675-9e07-f1a9f2a5e717"] }], "mendeley" : { "formattedCitation" : "(De Brouwere et al. 2014; Han and Price 2011; Price and Han 2011; Silva and Cerejeira 2015; Vallotton and Price 2016)", "manualFormatting" : "(Han and Price 2011; Price and Han 2011; Silva and Cerejeira 2015; Vallotton and Price 2016)", "plainTextFormattedCitation" : "(De Brouwere et al. 2014; Han and Price 2011; Price and Han 2011; Silva and Cerejeira 2015; Vallotton and Price 2016)", "previouslyFormattedCitation" : "(De Brouwere et al. 2014; Han and Price 2011; Price and Han 2011; Silva and Cerejeira 2015; Vallotton and Price 2016)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }], and mixtures in residential indoor air [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.scitotenv.2014.01.083", "ISBN" : "00489697", "ISSN" : "00489697", "PMID" : "24565859", "abstract" : "The maximum cumulative ratio (MCR) method allows the categorisation of mixtures according to whether the mixture is of concern for toxicity and if so whether this is driven by one substance or multiple substances. The aim of the present study was to explore, by application of the MCR approach, whether health risks due to indoor air pollution are dominated by one substance or are due to concurrent exposure to various substances. Analysis was undertaken on monitoring data of four European indoor studies (giving five datasets), involving 1800 records of indoor air or personal exposure.Application of the MCR methodology requires knowledge of the concentrations of chemicals in a mixture together with health-based reference values for those chemicals. For this evaluation, single

substance health-based reference values (RVs) were selected through a structured review process.The MCR analysis found high variability in the proportion of samples of concern for mixture toxicity. The fraction of samples in these groups of concern varied from 2% (Flemish schools) to 77% (EXPOLIS, Basel, indoor), the variation being due not only to the variation in indoor air contaminant levels across the studies but also to other factors such as differences in number and type of substances monitored, analytical performance, and choice of RVs. However, in 4 out of the 5 datasets, a considerable proportion of cases were found where a chemical-by-chemical approach failed to identify the need for the investigation of combined risk assessment.Although the MCR methodology applied in the current study provides no consideration of commonality of endpoints, it provides a tool for discrimination between those mixtures requiring further combined risk assessment and those for which a single-substance assessment is sufficient. ?? 2014 Elsevier B.V.", "author" : [{ "dropping-particle" : "", "family" : "Brouwere", "given" : "Katleen", "non-dropping-particle" : "De", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cornelis", "given" : "Christa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arvanitis", "given" : "Athanasios", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Brown", "given" : "Terry", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Crump", "given" : "Derrick", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harrison", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jantunen", "given" : "Matti", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Torfs", "given" : "Rudi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Science of the Total Environment", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2014"]] }, "page" : "267-276", "publisher" : "Elsevier B.V.", "title" : "Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air", "type" : "article-journal", "volume" : "479-480" }, "uris" : ["http://www.mendeley.com/documents/?uuid=88b4562e-de8c-4ca9-a413-b89213445bba"] }], "mendeley" : { "formattedCitation" : "(De Brouwere et al. 2014)", "plainTextFormattedCitation" : "(De Brouwere et al. 2014)", "previouslyFormattedCitation" : "(De Brouwere et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }].

The present study applied the MCR approach on a group of six phthalates from the National Health and Nutrition Examination Survey (NHANES) for the years 2013 and 2014. Reverse dosimetry techniques were used to reconstruct individuals' phthalate exposures from data using metabolite concentrations in their urine and information about their physiologies and demographics [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.yrtph.2014.04.019", "ISSN" : "10960295", "PMID" : "24815596", "abstract" : "Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6. years and older, as well as for men and women of approximate reproductive age (18-39. years), and children (6-11. years). Median HQs ranged from

<0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just > 1.0), and were driven by DEHP and DBP exposures. ?? 2014.", "author" : [{ "dropping-particle" : "", "family" : "Christensen", "given" : "Krista L Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Makris", "given" : "Susan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lorber", "given" : "Matthew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Regulatory Toxicology and Pharmacology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "380-389", "publisher" : "Elsevier Inc.", "title" : "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment", "type" : "article-journal", "volume" : "69" }, "uris" : ["http://www.mendeley.com/documents/?uuid=aab6a7b4-0ebc-4b3d-b1e7-c61e39c01d75"] }], "mendeley" : { "formattedCitation" : "(Christensen et al. 2014)", "plainTextFormattedCitation" : "(Christensen et al. 2014)", "previouslyFormattedCitation" : "(Christensen et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Using hazard information from each phthalate, MCR values were constructed. Results are presented by age, gender, and ethnicity.

METHODS

NHANES Data Set

Phthalate biomarker data came from the 2013-2014 cycle of NHANES [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013", "accessed" : { "date-parts" : [["2017", "1", "3"]] }, "author" : [{ "dropping-particle" : "", "family" : "CDC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Preventio", "id" : "ITEM-1", "issued" : { "date-parts" : [["2016"]] }, "title" : "No Title", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0f563aee-2cb4-45ca-bda7-b2388756f1a0"] }], "mendeley" : { "formattedCitation" : "(CDC 2016b)", "plainTextFormattedCitation" : "(CDC 2016b)", "previouslyFormattedCitation" : "(CDC 2016b)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. NHANES is a nationwide survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and is representative of the general non-institutionalized, civilian population in the United States. This survey has a complex multistage, stratified, random sampling design based on the sampling of counties, households, and household members. NHANES gathers information through interviews, physical examinations, and laboratory tests. Samples of urine are collected from participants six years and older and samples of blood are collected from participants aged one year and older [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overviewlab.aspx?BeginYear=2013", "accessed" : { "date-parts" : [["2017", "5", "31"]] }, "author" : [{ "dropping-particle" : "", "family" : "CDC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "National Health and Nutrition Exmination Survey", "id" : "ITEM-1", "issued" : { "date-parts" : [["2016"]] }, "title" : "2013-2014 Laboratory Data Overview", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=de150e9e-8b9d-45fe-9288-44f9d5e9d5c7"] }], "mendeley" : { "formattedCitation" : "(CDC 2016a)", "plainTextFormattedCitation" : "(CDC 2016a)", "previouslyFormattedCitation" : "(CDC 2016a)" }, "properties" : { "noteIndex" : 0 }, "schema" :

"https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Urine samples from a subset of participants were analyzed for metabolites of phthalates. Of the 2,777 participants sampled for phthalate analysis, 82 participants were missing a necessary metabolite concentration, and an additional 32 were missing either height or weight information. Thus, there were data from a total of 2,663 participants from the 2013-2014 NHANES cycle used in this analysis.

The six phthalates and associated metabolites included our analysis were di-n-butyl phthalate (DBP) (with metabolite MBP), diisobutyl phthalate (DIBP) (with metabolite MIBP), butyl benzyl phthalate (BBP) (with metabolite MBZP), di(2-ethylhexyl) phthalate (DEHP) (with metabolites MECPP, MEOHP, MEHHP, and MEHP), diisononyl phthalate (DINP) (with metabolites MINP and MCOP), and diisodecyl phthalate (DIDP) (with metabolite MCNP) (Table 1). At the time of this writing, the 2013-2014 NHANES cycle constitutes the most recent publically available NHANES biomonitoring data for these compounds. This combination of phthalates has been explored in previous works [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/jes.2014.24", "ISSN" : "1559-064X", "PMID" : "24756100", "abstract" : "As regulatory initiatives increasingly call for an understanding of the cumulative risks from chemical mixtures, evaluating exposure data from large biomonitoring programs, which may inform these cumulative risk assessments, will improve the understanding of occurrence and patterns of coexposures. Here we have analyzed the urinary metabolite data for six phthalates (di-butyl phthalate; di-isobutyl phthalate; butyl-benzyl phthalate; bis(2-ethylhexyl) phthalate; di-isononyl phthalate; and di-isodecyl phthalate) in the 2007/2008 National Health and Nutrition Examination Survey (NHANES) data set. For the total data set (N=2604), the co-occurrence of multiple phthalates at the upper percentile of exposure was infrequent. There were no individuals in the NHANES sample who were exposed to >95th percentiles for all six phthalates. For 75% of individuals, none of the six phthalates were above the 95th percentile of their respective exposure distributions. These data suggest that high exposure to multiple phthalates is infrequent in the NHANES population. This analysis solely focused on the pattern of contribution of individual phthalates to total exposure. It did not address the pattern of contribution to potential risk. The approach presented could potentially be used to provide insight into understanding the coexposure patterns for other chemicals.", "author" : [{ "dropping-particle" : "", "family" : "Qian", "given" : "Hua", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Min", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kransler", "given" : "Kevin M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zaleski", "given" : "Rosemary T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of exposure science & environmental epidemiology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2015"]] }, "page" : "249-55", "publisher" : "Nature Publishing Group", "title" : "Assessment of chemical coexposure patterns based upon phthalate biomonitoring data within the 2007/2008 National Health and Nutrition Examination Survey.", "type" : "article-journal", "volume" : "25" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e51515b4-9d5d-4e04-a1b8-c76d6c9cdaa4"] }], "mendeley" : { "formattedCitation" : "(Qian et al. 2015)", "plainTextFormattedCitation" : "(Qian et al. 2015)", "previouslyFormattedCitation" : "(Qian et al. 2015)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }] and is a slight expansion on the five phthalates investigated by Christensen et al. [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.yrtph.2014.04.019", "ISSN" : "10960295", "PMID" : "24815596", "abstract" : "Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using

urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6. years and older, as well as for men and women of approximate reproductive age (18-39. years), and children (6-11. years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just > 1.0), and were driven by DEHP and DBP exposures. ?? 2014.", "author" : [{ "dropping-particle" : "", "family" : "Christensen", "given" : "Krista L Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Makris", "given" : "Susan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lorber", "given" : "Matthew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Regulatory Toxicology and Pharmacology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "380-389", "publisher" : "Elsevier Inc.", "title" : "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment", "type" : "article-journal", "volume" : "69" }, "uris" : ["http://www.mendeley.com/documents/?uuid=1e16b722-485c-44b3-954e-d55f380fd00b"] }], "mendeley" : { "formattedCitation" : "(Christensen et al. 2014)", "plainTextFormattedCitation" : "(Christensen et al. 2014)", "previouslyFormattedCitation" : "(Christensen et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }].

Daily Intake Dose

Internal Daily Intake (DI) doses of phthalates for NHANES participants were calculated using the methodology presented in Christensen et al. [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.yrtph.2014.04.019", "ISSN" : "10960295", "PMID" : "24815596", "abstract" : "Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6. years and older, as well as for men and women of approximate reproductive age (18-39. years), and children (6-11. years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just > 1.0), and were driven by DEHP and DBP exposures. ?? 2014.", "author" : [{ "dropping-particle" : "", "family" : "Christensen", "given" : "Krista L Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Makris", "given" : "Susan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lorber", "given" : "Matthew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Regulatory Toxicology and Pharmacology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "380-389", "publisher" : "Elsevier Inc.", "title" : "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment", "type" : "article-journal", "volume" : "69" }, "uris" : ["http://www.mendeley.com/documents/?uuid=1e16b722-485c-44b3-954e-d55f380fd00b"] }],

"mendeley" : { "formattedCitation" : "(Christensen et al. 2014)", "plainTextFormattedCitation" : "(Christensen et al. 2014)", "previouslyFormattedCitation" : "(Christensen et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. In brief, the daily intake was calculated through adjusting metabolite concentrations of phthalates by creatinine concentrations while incorporating other variables such as daily creatinine excretion rates, the molar fraction of a given metabolite that was excreted, and information about the molecular weights of the metabolites and their parent phthalates. Under the assumption of steady state exposures, the DI for each participant i and metabolite k originating from parent phthalate j was calculated using the following equation:

$$DI_{i,j,k} = \left(\left[100 * \left(Met_{i,k}/Cr_i\right) * CE_i\right]/\left[F_{UE,i,k} * 1000\right]\right) \times \left(MW_{i,j}/MW_{i,j,k}\right) \quad [1]$$

where $DI_{i,j,k}$ ($\mu g/kg/d$) in urine is the daily intake dose for metabolite k, 100 is a unit conversion, $Met_{i,k}$ (ng/mL) is the metabolite concentration as given in the NHANES data set, Cr_i (mg/dL) is the creatinine concentration in urine as given in the NHANES data set, CE_i ($mg/kg/d$) is the creatinine excretion per day as calculated by Mage et al. [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.jes.7500614", "ISBN" : "1559-0631", "ISSN" : "1559-0631", "PMID" : "17878925", "abstract" : "A urine contaminant concentration per se has uncertain meaning for human health because of dilution by hydration. However, the estimation of the health-related daily intake dose of pollutant (mg/kg/day) that equilibrates with a spot urinary concentration of a pesticide residue or metabolite, or other analyte, can be made using creatinine-corrected toxicant levels (mg analyte/mg creatinine) multiplied by an estimate of the subjects' expected creatinine excretion rates (mg creatinine/kg/day). The objective was to develop a set of equations predicting a person's expected daily creatinine excretion (mg/kg) as a function of age, gender, race and morphometry, from birth to old age. We review the creatinine excretion literature where infants, children and adults provided 24 h total urine samples for creatinine analysis. Equations are developed for infants (<or=3 years), children (3-18 years) and adults (>or=18 years) that match at 3 and 18 years. A series of equations that estimate daily creatinine excretion (mg/day) are developed that are piecewise continuous from birth through infancy through adolescence and through adulthood for males and females, and Black and White races. Complicating factors such as diet, health status and obesity are discussed. We propose that these equations, with caveat, can now be used with measured urine concentrations to consistently estimate the corresponding equilibrium intake doses of toxicants at ages from birth to 92 years for the healthy non-obese. We recommend that this system of equations be considered for future development and reporting of applied doses in mg/kg/day of pollutants and toxicants that are measured in urine samples, as in the National Health and Nutrition Examination Survey.", "author" : [{ "dropping-particle" : "", "family" : "Mage", "given" : "David T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Allen", "given" : "Ruth H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kodali", "given" : "Anuradha", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of exposure science & environmental epidemiology", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2008"]] }, "page" : "360-368", "title" : "Creatinine corrections for estimating children's and adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine concentrations.", "type" : "article-journal", "volume" : "18" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0e27aba3-4f40-4e4a-93fe-cc6e7f74c5b9"] }], "mendeley" : { "formattedCitation" : "(Mage et al. 2008)", "plainTextFormattedCitation" : "(Mage et al. 2008)", "previouslyFormattedCitation" : "(Mage et al. 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }] using information about a participant's age, ethnicity, gender, weight, and height, $F_{UE,i,k}$ (unitless) is the molar fraction of metabolite excreted, 1000 is a unit

conversion, $MW_{i,j}$ $(\mathrm{mg/mol})$ is the molecular weight of the parent phthalate, and $MW_{i,j,k}$ $(\mathrm{mg/mol})$ is the molecular weight of the metabolite (Table S1). Among the multiple metabolites which have the same parent phthalate (i.e. DEHP and DINP), within an individual i, the value of $DI_{i,j}$ was calculated by taking a weighted average of the values of $DI_{i,j,k}$ estimated from each metabolite k using $F_{UE,i,k}$ [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.yrtph.2014.04.019", "ISSN" : "10960295", "PMID" : "24815596", "abstract" : "Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6. years and older, as well as for men and women of approximate reproductive age (18-39. years), and children (6-11. years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just > 1.0), and were driven by DEHP and DBP exposures. ?? 2014.", "author" : [{ "dropping-particle" : "", "family" : "Christensen", "given" : "Krista L Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Makris", "given" : "Susan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lorber", "given" : "Matthew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Regulatory Toxicology and Pharmacology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "380-389", "publisher" : "Elsevier Inc.", "title" : "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment", "type" : "article-journal", "volume" : "69" }, "uris" : ["http://www.mendeley.com/documents/?uuid=aab6a7b4-0ebc-4b3d-b1e7-c61e39c01d75"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/jes.2014.24", "ISSN" : "1559-064X", "PMID" : "24756100", "abstract" : "As regulatory initiatives increasingly call for an understanding of the cumulative risks from chemical mixtures, evaluating exposure data from large biomonitoring programs, which may inform these cumulative risk assessments, will improve the understanding of occurrence and patterns of coexposures. Here we have analyzed the urinary metabolite data for six phthalates (di-butyl phthalate; di-isobutyl phthalate; butyl-benzyl phthalate; bis(2-ethylhexyl) phthalate; di-isononyl phthalate; and di-isodecyl phthalate) in the 2007/2008 National Health and Nutrition Examination Survey (NHANES) data set. For the total data set (N=2604), the co-occurrence of multiple phthalates at the upper percentile of exposure was infrequent. There were no individuals in the NHANES sample who were exposed to >95th percentiles for all six phthalates. For 75% of individuals, none of the six phthalates were above the 95th percentile of their respective exposure distributions. These data suggest that high exposure to multiple phthalates is infrequent in the NHANES population. This analysis solely focused on the pattern of contribution of individual phthalates to total exposure. It did not address the pattern of contribution to potential risk. The approach presented could potentially be used to provide insight into understanding the coexposure patterns for other chemicals.", "author" : [{ "dropping-particle" : "", "family" : "Qian", "given" : "Hua", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Min", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kransler", "given" : "Kevin M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zaleski", "given" : "Rosemary T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of exposure science & environmental

epidemiology", "id" : "ITEM-2", "issue" : "3", "issued" : { "date-parts" : [["2015"]] }, "page" : "249-55", "publisher" : "Nature Publishing Group", "title" : "Assessment of chemical coexposure patterns based upon phthalate biomonitoring data within the 2007/2008 National Health and Nutrition Examination Survey.", "type" : "article-journal", "volume" : "25" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e51515b4-9d5d-4e04-a1b8-c76d6c9cdaa4"] }], "mendeley" : { "formattedCitation" : "(Christensen et al. 2014; Qian et al. 2015)", "plainTextFormattedCitation" : "(Christensen et al. 2014; Qian et al. 2015)", "previouslyFormattedCitation" : "(Christensen et al. 2014; Qian et al. 2015)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. The weighted average was determined using the following equation:

$$DI_{i,j} = \sum_{k=1}^{n_k} \left(DI_{i,j,k} \times \frac{F_{UE,i,k}}{\sum_{l=1}^{n_k} F_{UE,i,l}} \right), \quad [2]$$

where $DI_{i,j}$ is the daily intake dose for phthalate j and n_k is the number of metabolites for a given parent phthalate. In this work, $n_k \in \{1,2,4\}$.

We used the NHANES convention of setting metabolite concentrations below the Limit of Detection (LOD) to $LOD/\sqrt{2}$. Table 1 gives the LOD for each metabolite and the number (and percentage) of participants with metabolites below the LODs. Table 1 indicates the majority of the metabolites were detectable in more than 97% of the surveyed participants. The predictions of $DI_{i,j}$ for each participant, the measurements of metabolite concentrations obtained from NHANES, and the physiological and demographic information used to determine $DI_{i,j}$ values are provided in the Supplemental Material.

Maximum Cumulative Ratio

The following equations were used to determine the values of HQ and HI for participant i and phthalate j for N phthalates:

$$HQ_{i,j} = DI_{i,j}/TDI_j \quad [3]$$

$$HQ_{M,i} = \max_{j\epsilon\{1,\ldots,N\}} HQ_{i,j} \quad [4]$$

$$HI_i = \sum_{j=1}^{N} HQ_{i,j} \quad [5]$$

There were six phthalates used in this analysis (i.e. $N = 6$) and HQ_M quantifies the maximum HQ among the six phthalates for participant i. The TDIs used in this study and their references are given in Table 1. Five of the six were taken from [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.yrtph.2014.04.019", "ISSN" : "10960295", "PMID" : "24815596", "abstract" : "Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate

reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6. years and older, as well as for men and women of approximate reproductive age (18-39. years), and children (6-11. years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just > 1.0), and were driven by DEHP and DBP exposures. ?? 2014.", "author" : [{ "dropping-particle" : "", "family" : "Christensen", "given" : "Krista L Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Makris", "given" : "Susan L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lorber", "given" : "Matthew", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Regulatory Toxicology and Pharmacology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "380-389", "publisher" : "Elsevier Inc.", "title" : "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment", "type" : "article-journal", "volume" : "69" }, "uris" : ["http://www.mendeley.com/documents/?uuid=aab6a7b4-0ebc-4b3d-b1e7-c61e39c01d75"] }], "mendeley" : { "formattedCitation" : "(Christensen et al. 2014)", "plainTextFormattedCitation" : "(Christensen et al. 2014)", "previouslyFormattedCitation" : "(Christensen et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }] with DIDP taken from [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "CPSC", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-1", "issued" : { "date-parts" : [["2010"]] }, "publisher-place" : "Bethesda, Maryland", "title" : "Overview of Phthalates Toxicity", "type" : "article-journal" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b5113798-00c6-4f04-b89f-33bdc750707b"] }], "mendeley" : { "formattedCitation" : "(CPSC 2010)", "plainTextFormattedCitation" : "(CPSC 2010)", "previouslyFormattedCitation" : "(CPSC 2010)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }].

The MCR is a function of the doses that reaches an exposed individual; as a result, values of MCR will vary across individuals in an exposed population ranging from one to N (i.e. $MCR_i \in [1, N]$), where N is the number of chemicals considered in the assessment. A value close to one indicates that one chemical was responsible for almost all of the individual's cumulative risk, and a value of N indicates that the individual receives an equitoxic dose from all chemicals. The value of the MCR can be readily determined using the metrics HI and HQ used for screening assessments. The value of MCR for an individual i in an exposed population is defined as:

$$MCR_i = HI_i / HQ_{M,i} \quad [6]$$

The values of HI and the MCR can be used to evaluate cumulative exposures in a number of ways. The correlation of $MCR - 1$ against HI is a useful criterion in evaluating cumulative exposures. A negative correlation (i.e. $MCR - 1$ declines as HI increases) indicates that the individuals most at risk from cumulative exposures received the majority of their risks from a single chemical. A positive correlation indicates that cumulative exposures to multiple chemicals drove the highest risks in the population. A negative correlation suggests that risk mitigation should focus on the population groups with high exposures to individual phthalates. A positive correlation indicates that tracking cumulative exposures is required to fully characterize risks.

The determination of the values of HI and MCR enables categorization of the surveyed participants into four groups [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1186/2190-4715-24-34", "ISSN" : "2190-4715", "abstract" : "Background: A decision tree has been developed for evaluating risks posed by combined exposures to multiple chemicals. The decision tree divides combined exposures of humans and ecological receptors into groups where one or more

components are a concern by themselves, where risks from the combined exposures are of low concern, and where there is a concern for the effects from the combined exposures but not from individual chemicals. This paper applies the decision tree to real-world examples of exposures to multiple chemicals, evaluates the usefulness of the approach, and identifies issues arising from the application. Results: The decision tree was used to evaluate human health and ecological effects from the combined exposure to 559 mixtures of substances measured in surface waters and effluents. The samples contained detectable levels of 2 to 49 substances. The key findings were, 1) the need for assessments of the combined exposures varied for ecological and human health effects and with the source of the monitoring data, 2) the majority of the toxicity came from one chemical in 44% of the exposures (human health) and 60% of exposures (ecological effects), 3) most cases, where risk from combined exposures was a concern, would have been identified using chemical-by-chemical assessments. Finally, the tree identified chemicals where data on the mode of action would be most useful in refining an assessment. Conclusions: The decision tree provided useful information on the need for combined risk assessments and guidance on the questions that should be addressed in future research. \u00a9 2012 Price et al.; licensee Springer.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "X.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Junghans", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kunz", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Watts", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Leverett", "given" : "D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Sciences Europe", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2012"]] }, "page" : "34", "title" : "An application of a decision tree for assessing effects from exposures to multiple substances to the assessment of human and ecological effects from combined exposures to chemicals observed in surface waters and waste water effluents", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dcc264b9-9e79-4001-a5a2-86bc54009a45"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1186/2190-4715-24-26", "ISSN" : "2190-4715", "abstract" : "Background: The Cefic Mixtures Industry Ad-hoc Team (MIAT) has investigated how risks from combined exposures can be effectively identified and managed using concepts proposed in recent regulatory guidance, new advances in risk assessment, and lessons learned from a Cefic-sponsored case study of mixture exposures. Results: A series of tools were created that include: a decision tree, a system for grouping exposures, and a graphical tool (the MCR-HI plot). The decision tree allows the division of combined exposures into different groups, exposures where one or more individual components are a concern, exposures that are of low concern, and exposures that are a concern for combined effects but not for the effects of individual chemicals. These tools efficiently use available data, identify critical data gaps for combined assessments, and prioritize which chemicals require detailed toxicity information. The tools can be used to address multiple human health endpoints and ecological effects. Conclusion: The tools provide a useful approach for assessing risks associated with combined exposures to multiple chemicals. \u00a9 2012 Price et al.; licensee Springer.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dhein", "given" : "Ellen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hamer", "given" : "Mick", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Heneweer", "given" : "Marjoke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Junghans", "given" : "Marion", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kunz",

"given" : "Petra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Magyar", "given" : "Csilla", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Penning", "given" : "Holger", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rodriguez", "given" : "Carlos", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Sciences Europe", "id" : "ITEM-2", "issue" : "1", "issued" : { "date-parts" : [["2012"]] }, "page" : "26", "publisher" : "Environmental Sciences Europe", "title" : "A decision tree for assessing effects from exposures to multiple substances", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8be8c2fa-2976-4ac9-83d5-b9de76e47b8d"] }], "mendeley" : { "formattedCitation" : "(Price et al. 2012b, 2012a)", "plainTextFormattedCitation" : "(Price et al. 2012b, 2012a)", "previouslyFormattedCitation" : "(Price et al. 2012b, 2012a)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Group I are those participants having one or more phthalate exposures that exceeds the respective benchmarks ($HQ_M > 1$). Group II are participants with minimal risks under an additive model of toxicity ($HI \leq 1$). The participants that did not fall into either Groups I or II, are participants with cumulative phthalate exposures that are a potential concern. However, none of the phthalates would have been identified under a single-chemical assessment. These mixtures are identified as Group III. Group III can be divided into two subgroups. Group IIIA includes those mixtures with an $MCR < 2$. In these mixtures, the majority of the risk to a participant was driven by one phthalate. The remaining mixtures fall into Group IIIB where no single phthalate results in the majority of risk. In this study, MCR is determined for each participant. The relative number of participants falling in the groups along with the ranges of HI for each group can provide additional insight on the patterns of exposure. Plotting the values of $MCR - 1$ versus HI for the surveyed participants on a log-log plot results in the four groups falling into contiguous regions.

The pattern of exposures received by participants in Group III potentially provides insights into specific combinations of chemicals that result in cumulative exposures of potential concern that would be missed in a chemical-by-chemical approach [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1186/2190-4715-24-34", "ISSN" : "2190-4715", "abstract" : "Background: A decision tree has been developed for evaluating risks posed by combined exposures to multiple chemicals. The decision tree divides combined exposures of humans and ecological receptors into groups where one or more components are a concern by themselves, where risks from the combined exposures are of low concern, and where there is a concern for the effects from the combined exposures but not from individual chemicals. This paper applies the decision tree to real-world examples of exposures to multiple chemicals, evaluates the usefulness of the approach, and identifies issues arising from the application. Results: The decision tree was used to evaluate human health and ecological effects from the combined exposure to 559 mixtures of substances measured in surface waters and effluents. The samples contained detectable levels of 2 to 49 substances. The key findings were, 1) the need for assessments of the combined exposures varied for ecological and human health effects and with the source of the monitoring data, 2) the majority of the toxicity came from one chemical in 44% of the exposures (human health) and 60% of exposures (ecological effects), 3) most cases, where risk from combined exposures was a concern, would have been identified using chemical-by-chemical assessments. Finally, the tree identified chemicals where data on the mode of action would be most useful in refining an assessment. Conclusions: The decision tree provided useful information on the need for combined risk assessments and guidance on the questions that should be addressed in future research. \u00a9 2012 Price et al.; licensee Springer.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "X.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Junghans", "given" : "M.", "non-dropping-

particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kunz", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Watts", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Leverett", "given" : "D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Sciences Europe", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2012"]] }, "page" : "34", "title" : "An application of a decision tree for assessing effects from exposures to multiple substances to the assessment of human and ecological effects from combined exposures to chemicals observed in surface waters and waste water effluents", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dcc264b9-9e79-4001-a5a2-86bc54009a45"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1021/acs.est.5b06267", "ISSN" : "0013-936X", "author" : [{ "dropping-particle" : "", "family" : "Vallotton", "given" : "Nathalie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Science & Technology", "id" : "ITEM-2", "issue" : "10", "issued" : { "date-parts" : [["2016"]] }, "page" : "5286-5293", "title" : "Use of the Maximum Cumulative Ratio As an Approach for Prioritizing Aquatic Coexposure to Plant Protection Products: A Case Study of a Large Surface Water Monitoring Database", "type" : "article-journal", "volume" : "50" }, "uris" : ["http://www.mendeley.com/documents/?uuid=27bc6604-14bf-4675-9e07-f1a9f2a5e717"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1186/2190-4715-24-26", "ISSN" : "2190-4715", "abstract" : "Background: The Cefic Mixtures Industry Ad-hoc Team (MIAT) has investigated how risks from combined exposures can be effectively identified and managed using concepts proposed in recent regulatory guidance, new advances in risk assessment, and lessons learned from a Cefic-sponsored case study of mixture exposures. Results: A series of tools were created that include: a decision tree, a system for grouping exposures, and a graphical tool (the MCR-HI plot). The decision tree allows the division of combined exposures into different groups, exposures where one or more individual components are a concern, exposures that are of low concern, and exposures that are a concern for combined effects but not for the effects of individual chemicals. These tools efficiently use available data, identify critical data gaps for combined assessments, and prioritize which chemicals require detailed toxicity information. The tools can be used to address multiple human health endpoints and ecological effects. Conclusion: The tools provide a useful approach for assessing risks associated with combined exposures to multiple chemicals. \u00a9 2012 Price et al.; licensee Springer.", "author" : [{ "dropping-particle" : "", "family" : "Price", "given" : "Paul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dhein", "given" : "Ellen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hamer", "given" : "Mick", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Heneweer", "given" : "Marjoke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Junghans", "given" : "Marion", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kunz", "given" : "Petra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Magyar", "given" : "Csilla", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Penning", "given" : "Holger", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rodriguez", "given" : "Carlos", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Sciences Europe", "id" : "ITEM-3", "issue" : "1", "issued" : { "date-parts" : [["2012"]] }, "page" : "26", "publisher" : "Environmental Sciences Europe", "title" : "A decision tree for assessing effects from exposures to multiple substances", "type" : "article-journal", "volume" : "24" }, "uris" : [

"http://www.mendeley.com/documents/?uuid=8be8c2fa-2976-4ac9-83d5-b9de76e47b8d"] }], "mendeley" : { "formattedCitation" : "(Price et al. 2012b, 2012a; Vallotton and Price 2016)", "plainTextFormattedCitation" : "(Price et al. 2012b, 2012a; Vallotton and Price 2016)", "previouslyFormattedCitation" : "(Han and Price 2011; Vallotton and Price 2016)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }].

NHANES reports the demographics of the surveyed participants. This allows a determination of whether there are population groups that are at elevated risk. In this study we investigated age by dividing the population into school age, 6 to 17 years of age, and adults, 18 and above years of age. (NHANES does not include phthalate biomonitoring data on children under the age of six years). The population was also divided by gender and ethnicity (i.e., Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other – including multi-racial).

The impact of two alternative approaches for evaluating hazard were investigated. First, MCNP the metabolite of DIDP and MINP, one of the two metabolites of DINP were omitted from the assessment as was done in Christensen et al. (2014). Secondly, non-detects were set to zero. All analyses and visualizations were conducted in R (version 3.2.2) using the packages ggplot2 (version 2.2.0) and survey (version 3.31).

RESULTS

Visualizing hazard and the Maximum Cumulative Ratio

The MCR calculated among the 2,663 participants ranged from 1.1 to 3.6. Because six phthalates were considered, MCR can range between one and 6. The finding that MCR values were all below 3.6 indicated that none of the exposed participants received the same level of risk from the six phthalates. That is, for each subject, a subgroup of phthalates had a dominate influence on the participant's value of HI. HI ranged from 0.01 to 5.0 but exceeded one for only 21 (0.8%) of surveyed participants. The values of HQ, HI, and MCR for each individual are provided in the Supplemental Material.

Figure 1 presents a plot of the log of $MCR - 1$ versus the log of HI for the 2,663 participants. In this plot the lower the value on the vertical axis for a participant (i.e. the $MCR - 1$ axis), the more their risk was dominated by exposures to one phthalate. To aid in this understanding the vertical axis also provides the percent contribution of HI from the HQ_M. There were 12 participants in Group I, 2,642 participants in Group II, six participants in Group IIIA, and three participants in Group IIIB (Table 2). Group I designates participants whose $HQ_M > 1$ and therefore would be successfully identified in a chemical-by-chemical assessment. The average (range) of HI values among surveyed participants in Group I was 2.2 (1.1-5.0). There were fewer participants in Group III than Group I. Group III identifies participants with a potentially hazardous internal dose that could only be properly identified through a cumulative assessment. The average (range) of HI values among surveyed participants in Group III was 1.1 (1.0-1.4).

Phthalates that drive cumulative exposures

In Figure 1 the data are identified by which phthalate produced the HQ_M. Only four of the six phthalates produced HQ_M in at least one participant. The collective internal doses of most participants were either driven by DPB, DINP, DIDP, or DEHP (Table2). (BBP or DIBP did not produce HQ_M for any participant.) Although DBP and DINP produced the HQ_M for the vast majority of participants, the frequency at which certain phthalates produced the HQ_M changed as a function of HI and Group. Among those participants with lower HI values (i.e. Group II), internal dosages were primarily driven by DBP.

Among participants at large HI values (i.e. Groups I and III) dosages were primarily driven by DEHP and DINP. Among Groups I and III, the odds of hazardous mixtures being driven by one chemical was 4:3. Group III (i.e. those participants that would be missed by a chemical-by-chemical assessment) and Group I (i.e. participants that would be correctly identified as at-risk by a chemical-by-chemical assessment) were dominated by DINP.

For six phthalates, there are 15 possible unique pairs. However, this analysis suggested that some pairs of phthalates were more important in terms of defining cumulative risk than others. The top two phthalates in each of the 21 participants with $HI > 1$ were determined. Table 3 presents the distribution of these pairs of phthalates. As Table 3 indicates, only four of the six phthalates appeared in the top two HQs for the surveyed participants among the 21 participants with $HI > 1$. A total of 19 of the 21 pairs involve only three phthalates: DEHP, DINP, and DIDP.

The decline of MCR with HI

There was a distinct downward trend between HI and MCR when both parameters were plotted on a log scale. Figure 1 includes a linear regression model with 95% confidence intervals. Although this work does not prove the linearity of this relationship as fit with linear regression parameters (Table S2), this trend elucidates the relationship between the two parameters and informs us about the importance of a single chemical in determining cumulative risk. As HI values increase, the values of MCR tend to decrease. That is, as hazards to individual phthalates increase, the participant was more likely to have a single hazard quotient dominate their HI. Among participants, the data were subset to the individual phthalates that produced the HQ_M and a linear regression model was refit. After the refitting, HQ_M from DEHP, DBP, and DINP produced a statistically significant negative correlation between HI and MCR while DIDP did not produce a statistically significant negative correlation (Figure S1). This lack of significance was likely due to the limited number of surveyed participants where DIDP produced the HQ_M (Table S2).

This trend of increasing dominance by a single phthalate could be seen within select participants (Figure 2). Among ten participants with HI values at or just above the 50th percentile of HI for the population, few of the phthalates had HQ values that make up the majority of the participants' HIs. This was evidenced by the mean MCR value (2.1). Among ten participants with HI values at, or just above, the 99th percentile of HI, most had a phthalate that provides more than 50% of their HI values. The median MCR values for the 50th and 99th percentile groups were 2.1 and 1.2, respectively. Thus, the median MCR values for the individuals just above the 50th percentile was 0.8 times larger than those just above the 99th percentile, meaning that participants at the higher ends of hazard are driven more by individual chemicals within a given mixture compared to participants in the midrange of hazard.

The effect of demographics on MCR and HI

After adjusting for the NHANES study design using weights, there was a statistically significant difference in the HI means between children (aged six to 17 years) and adults (aged 18+ years) (mean 0.19 and 0.14, respectively) ($p < 0.001$) (Table S3). The numbers and percent of children and adults with an $HI > 1$ were eight (1.1%) and 13 (0.7%), respectively (Table 4). After adjusting for NHANES weights, there was no statistical difference in the proportion of children versus adults with $HI > 1$ (Table S3). However, the small fraction of those with $HI > 1$ limits our ability to identify differences. Among children with $HI \leq 1$, MCR ranged from 1.1 – 3.5 compared with 1.1 – 3.6 among adults. Among children with $HI > 1$, MCR ranged from 1.1 – 2.3 compared with 1.1 – 2.1 among adults. Within both age groups the negative correlation of $MCR - 1$ and HI was statistically significant (Table S2, Figure S2).

Although disparities of exposure to phthalates based on gender, particularly when presented by ethnicity, have been reported [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : {

"DOI" : "10.1186/s12940-015-0043-6", "ISBN" : "1476-069X (Electronic)\\r1476-069X (Linking)", "ISSN" : "1476-069X", "PMID" : "26174070", "abstract" : "BACKGROUND: Diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP) are industrial chemicals found in consumer products that may increase risk of adverse health effects. Although use of personal care/beauty products is known to contribute to phthalate exposure, no prior study has examined feminine hygiene products as a potential phthalate source. In this study, we evaluate whether vaginal douching and other feminine hygiene products increase exposure to phthalates among US reproductive-aged women. METHODS: We conducted a cross-sectional study on 739 women (aged 20\u201349) from the National Health and Nutrition Examination Survey 2001\u20132004 to examine the association between self-reported use of feminine hygiene products (tampons, sanitary napkins, vaginal douches, feminine spray, feminine powder, and feminine wipes/towelettes) with urinary concentrations of monoethyl phthalate (MEP) and mono-n-butyl phthalate (MnBP), metabolites of DEP and DnBP, respectively. RESULTS: A greater proportion of black women than white and Mexican American women reported use of vaginal douches, feminine spray, feminine powder, and wipes/towelettes in the past month whereas white women were more likely than other racial/ethnic groups to report use of tampons ($p < 0.05$). Douching in the past month was associated with higher concentrations of MEP but not MnBP. No other feminine hygiene product was significantly associated with either MEP or MnBP. We observed a dose\u2013response relationship between douching frequency and MEP concentrations (p(trend) < 0.0001); frequent users (\u22652 times/month) had 152.2 % (95 % confidence intervals (CI): (68.2 %, 278.3 %)) higher MEP concentrations than non-users. We also examined whether vaginal douching mediates the relationship between race/ethnicity and phthalates exposures. Black women had 48.4 % (95 % CI: 16.8 %, 88.6 %; $p = 0.0002$) higher MEP levels than white women. Adjustment for douching attenuated this difference to 26.4 % (95 % CI:\u22120.9 %, 61.2 %; $p = 0.06$). Mediation effects of douching were statistically significant for black-white differences ($z = 3.71$, $p < 0.001$) but not for differences between Mexican Americans and whites ($z = 1.80$, $p = 0.07$). CONCLUSIONS: Vaginal douching may increase exposure to DEP and contribute to racial/ethnic disparities in DEP exposure. The presence of environmental chemicals in vaginal douches warrants further examination.", "author" : [{ "dropping-particle" : "", "family" : "Branch", "given" : "Francesca", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Woodruff", "given" : "Tracey J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mitro", "given" : "Susanna D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zota", "given" : "Ami R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health", "id" : "ITEM-1", "issued" : { "date-parts" : [["2015"]] }, "page" : "57", "publisher" : "Environmental Health", "title" : "Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001\u20132004", "type" : "article-journal", "volume" : "14" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9ff7811e-10d3-4358-926a-b0034d94ad25"] }], "mendeley" : { "formattedCitation" : "(Branch et al. 2015)", "plainTextFormattedCitation" : "(Branch et al. 2015)", "previouslyFormattedCitation" : "(Branch et al. 2015)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }], there was little evidence in gender differences observed in the cumulative risk indexes investigated in this study (Table S3). There were ten males with $HI > 1$ and eleven females with $HI > 1$. This difference was not statistically significant (Table S3). As with age, there is an inverse relationship between HI and MCR when the data were subset to each gender (Figure S3). The average HI (range) among women was 0.2 (0.01 – 5.0) while the average HI (range) among men was 0.2 (0.01 – 2.8). Among both females and males with $HI \leq 1$, MCR ranged from 1.1 – 3.6. Among females with $HI > 1$, MCR ranged from 1.1 – 2.3 compared with 1.1 – 2.1 among males. After adjusting for the study design, there was no statistically significant difference in the HI means between men and women (Table S3).

Lastly, MCR and HI plots can be presented by an NHANES ethnicity variable exploring Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other (including multi-racial) (Figure S4) ethnicities. There were no statistically significant differences in mean HI or in the proportions of participants with $HI > 1$ among ethnic groups (Table S3). Like the previous participant characteristics, there was a downward trend of MCR as a function of HI for all ethnic groups (Table S3).

The two alternative approaches produced similar results as the analyses presented here (Table S4). The lack of impact from dropping the two metabolites was expected since the HQ values for DIDP were small compared to those from DEHP, DPB, and DINP. Dropping MINP from the calculation of DINP did result in slightly higher predicted doses for that phthalate. The lack of impact from setting non-detects to zero was expected since detection limits for the phthalates are low in comparison to the compounds' toxicity standards.

DISCUSSION

This work investigated recent data on exposures to six phthalates. The data indicated that less than 1% of the surveyed participants (12 in Group I and 9 in Group III) had HI values of concern. While this percentage was small, it may correspond to a large number of individuals in the US population. The analysis also suggested that exposures of concern in some individuals would be missed if using a chemical-by-chemical exposure risk assessment (Group III). However, the analysis also showed that the participants in Group III tended to have smaller HI values than participants in Group I (average HI value of 1.1 versus 2.2, respectively). HI values in Group III did not exceed 1.4. Thus a phthalate-by-phthalate assessment approach that ignored additive effects of the combined exposures still identified the most at-risk participants. Among the 15 possible unique pairs of the six phthalates, only three pairs were strongly associated with values of $HI > 1$ (Table 3): DEHP:DINP, DINP:DIDP, and DIDP:DEHP. This suggests that toxicological studies of phthalate interactions should focus on the phthalates in these pairs. Finally, although the time period and set of metabolites differed, the absence of strong ethnicity and gender differences in these data disagree with earlier findings and may warrant additional study [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1186/s12940-015-0043-6", "ISBN" : "1476-069X (Electronic)\\r1476-069X (Linking)", "ISSN" : "1476-069X", "PMID" : "26174070", "abstract" : "BACKGROUND: Diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP) are industrial chemicals found in consumer products that may increase risk of adverse health effects. Although use of personal care/beauty products is known to contribute to phthalate exposure, no prior study has examined feminine hygiene products as a potential phthalate source. In this study, we evaluate whether vaginal douching and other feminine hygiene products increase exposure to phthalates among US reproductive-aged women. METHODS: We conducted a cross-sectional study on 739 women (aged 20\u201349) from the National Health and Nutrition Examination Survey 2001\u20132004 to examine the association between self-reported use of feminine hygiene products (tampons, sanitary napkins, vaginal douches, feminine spray, feminine powder, and feminine wipes/towelettes) with urinary concentrations of monoethyl phthalate (MEP) and mono-n-butyl phthalate (MnBP), metabolites of DEP and DnBP, respectively. RESULTS: A greater proportion of black women than white and Mexican American women reported use of vaginal douches, feminine spray, feminine powder, and wipes/towelettes in the past month whereas white women were more likely than other racial/ethnic groups to report use of tampons ($p < 0.05$). Douching in the past month was associated with higher concentrations of MEP but not MnBP. No other feminine hygiene product was significantly associated with either MEP or MnBP. We observed a dose\u2013response relationship between douching frequency and MEP concentrations (p(trend) < 0.0001); frequent users (\u22652 times/month) had 152.2 % (95 % confidence intervals (CI): (68.2 %, 278.3 %)) higher MEP concentrations than non-users. We also examined whether vaginal douching mediates the relationship between

race/ethnicity and phthalates exposures. Black women had 48.4 % (95 % CI: 16.8 %, 88.6 %; p = 0.0002) higher MEP levels than white women. Adjustment for douching attenuated this difference to 26.4 % (95 % CI:\u22120.9 %, 61.2 %; p = 0.06). Mediation effects of douching were statistically significant for black-white differences (z = 3.71, p < 0.001) but not for differences between Mexican Americans and whites (z = 1.80, p = 0.07). CONCLUSIONS: Vaginal douching may increase exposure to DEP and contribute to racial/ethnic disparities in DEP exposure. The presence of environmental chemicals in vaginal douches warrants further examination.", "author" : [{ "dropping-particle" : "", "family" : "Branch", "given" : "Francesca", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Woodruff", "given" : "Tracey J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mitro", "given" : "Susanna D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zota", "given" : "Ami R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health", "id" : "ITEM-1", "issued" : { "date-parts" : [["2015"]] }, "page" : "57", "publisher" : "Environmental Health", "title" : "Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001\u20132004", "type" : "article-journal", "volume" : "14" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9ff7811e-10d3-4358-926a-b0034d94ad25"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1289/ehp.1306681", "ISBN" : "8037776220", "ISSN" : "15529924", "PMID" : "24425099", "abstract" : "BACKGROUND: Phthalates are ubiquitous environmental contaminants. Because of potential adverse effects on human health, butylbenzyl phthalate [BBzP; metabolite, monobenzyl phthalate (MBzP)], di-n-butyl phthalate [DnBP; metabolite, mono-n-butyl phthalate (MnBP)], and di(2-ethylhexyl) phthalate (DEHP) are being replaced by substitutes including other phthalates; however, little is known about consequent trends in population-level exposures. OBJECTIVE: We examined temporal trends in urinary concentrations of phthalate metabolites in the general U.S. population and whether trends vary by sociodemographic characteristics. METHODS: We combined data on 11 phthalate metabolites for 11,071 participants from five cycles of the National Health and Nutrition Examination Survey (2001\u20132010). Percent changes and least square geometric means (LSGMs) were calculated from multivariate regression models. RESULTS: LSGM concentrations of monoethyl phthalate, MnBP, MBzP, and \u2211DEHP metabolites decreased between 2001\u20132002 and 2009\u20132010 [percent change (95% CI): \u201342% (\u201349, \u201334); \u201317% (\u201323, \u20139); \u201332% (\u201339, \u201323) and \u201337% (\u201346, \u201326), respectively]. In contrast, LSGM concentra- tions of monoisobutyl phthalate, mono(3-carboxypropyl) phthalate (MCPP), monocarboxyoctyl phthalate, and monocarboxynonyl phthalate (MCNP) increased over the study period [percent change (95% CI): 206% (178, 236); 25% (8, 45); 149% (102, 207); and 15% (1, 30), respectively]. Trends varied by subpopulations for certain phthalates. For example, LSGM concentrations of \u2211DEHP metabolites, MCPP, and MCNP were higher in children than adults, but the gap between groups narrowed over time (pinteraction < 0.01). CONCLUSIONS: Exposure of the U.S. population to phthalates has changed in the last decade. Data gaps make it difficult to explain trends, but legislative activity and advocacy campaigns by non- governmental organizations may play a role in changing trends.", "author" : [{ "dropping-particle" : "", "family" : "Zota", "given" : "Ami R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Calafat", "given" : "Antonia M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Woodruff", "given" : "Tracey J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-2", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "235-241", "title" : "Temporal trends in phthalate exposures: Findings from the national health and nutrition examination survey, 2001-2010", "type" : "article-journal", "volume" : "122" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d32ae744-e353-44f7-93fe-5754dc7cf8f2"] }], "mendeley" : { "formattedCitation" : "(Branch et al. 2015; Zota et al. 2014)",

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The total fraction of the survey population with $HI > 1$ was 0.8%. The probability of having $HI > 1$ appears to be similar for adults and children aged six years and older, males and females, and across different ethnicities. The hazards to participants in Groups I and III were largely driven by DINP. We found a significant negative correlation between the log $MCR - 1$ and the log of HI. This negative correlation implies that health impacts in the most at-risk portion of the population were largely driven by exposures to a single phthalate and not cumulative exposures to multiple phthalates.

This was the first application of the MCR approach to assess phthalate cumulative exposures. This was the second analysis to apply the MCR approach to biomonitoring data [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/jes.2012.74", "ISSN" : "1559-064X", "PMID" : "22781437", "abstract" : "Maximum cumulative ratio (MCR) is a person's cumulative exposure to multiple chemicals divided by the maximum chemical-specific exposure where exposure is expressed on a toxicologically equivalent basis. It is a tool for assessing the need for performing cumulative exposure assessments. In this paper, MCR values were calculated for the three groups of individuals with biomonitoring data of 26 dioxin-like compounds (DLCs) based on the World Health Organization toxic equivalent factors (TEFs). Although the two occupational groups have higher total toxicity equivalence (TEQ) levels than the NHANES group, average MCR values of the three groups are similar (3.5, 3.6, and 3.2). These MCR values are higher than those seen in our earlier studies, supporting the practice of performing cumulative assessments for DLCs. The MCR values also indicate that only 2-5 of the 26 chemicals make significant contributions to total TEQ values. Interestingly, MCR is negatively correlated with total TEQ (in all the three groups) and age (in the NHANES group). Additionally, MCR is lower in workers where occupational exposures are larger than background exposures. Although overall exposure is the first factor to consider in any mixtures assessment, this paper confirms the usefulness of MCR as a tool for analyzing the pattern of chemical-specific contributions to the total exposure levels of mixtures based on biomonitoring data when TEFs or similar approaches are available.", "author" : [{ "dropping-particle" : "", "family" : "Han", "given" : "Xianglu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Price", "given" : "Paul S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of exposure science & environmental epidemiology", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2013"]] }, "page" : "343-9", "publisher" : "Nature Publishing Group", "title" : "Applying the maximum cumulative ratio methodology to biomonitoring data on dioxin-like compounds in the general public and two occupationally exposed populations", "type" : "article-journal", "volume" : "23" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c1298fe7-b0c5-4454-b2c2-e15baeac76ea"] }], "mendeley" : { "formattedCitation" : "(Han and Price 2013)", "plainTextFormattedCitation" : "(Han and Price 2013)", "previouslyFormattedCitation" : "(Han and Price 2013)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }] and the first publication that applied MCR to biomonitoring data of short half-life compounds. This was the first work to explore the four groups defined by MCR and HI (e.g., Group I, Group II, Group IIIA, and Group IIIB) for estimated exposures using biomonitoring data. This was also the first work to use the graphing technique of visualizing both HI and the MCR on a log-log scale. By fitting both variables on log scales, the relationship between the two parameters were more clearly displayed and quantified (slope of a regression equation) than the approaches used in earlier publications (Price and Han, 2011, Han and Price, 2011).

Much of this work was based on approaches published by Qian et al. (2014) and Christensen et al. (2014). Christensen et al. combined cycles from 2005-2006 and 2007-2008 and explored five phthalates from eight metabolites. Qian et al. used only the 2007-2008 cycle and incorporated DIDP and

a second metabolite (i.e. MINP) of DINP for a total of six phthalates from ten metabolites. Christensen et al. investigated hazard while Qian et al. investigated dose. This work looked at the six phthalates chosen by Qian et al. while looking at measures of hazard like in Christensen et al. Our findings differ from these earlier works in some key ways. Christensen et al. found that overall hazard was mostly driven by DEHP with the averaged HI in the population being 0.3 with hazards mostly coming from exposures to DEHP and to a lesser extent DINP. In this study we found the average HI to be 0.15 with DINP now being the dominate contributor to participants with $HI > 1$. The drop in overall hazard as witnessed from drops in internal daily intake doses from 2005-2008 to 2013-2014 is in line with overall trends of declining levels of metabolites of some phthalates seen in other works [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1289/ehp.1306681", "ISBN" : "8037776220", "ISSN" : "15529924", "PMID" : "24425099", "abstract" : "BACKGROUND: Phthalates are ubiquitous environmental contaminants. Because of potential adverse effects on human health, butylbenzyl phthalate [BBzP; metabolite, monobenzyl phthalate (MBzP)], di-n-butyl phthalate [DnBP; metabolite, mono-n-butyl phthalate (MnBP)], and di(2-ethylhexyl) phthalate (DEHP) are being replaced by substitutes including other phthalates; however, little is known about consequent trends in population-level exposures. OBJECTIVE: We examined temporal trends in urinary concentrations of phthalate metabolites in the general U.S. population and whether trends vary by sociodemographic characteristics. METHODS: We combined data on 11 phthalate metabolites for 11,071 participants from five cycles of the National Health and Nutrition Examination Survey (2001\u20132010). Percent changes and least square geometric means (LSGMs) were calculated from multivariate regression models. RESULTS: LSGM concentrations of monoethyl phthalate, MnBP, MBzP, and \u2211DEHP metabolites decreased between 2001\u20132002 and 2009\u20132010 [percent change (95% CI): \u201342% (\u201349, \u201334); \u201317% (\u201323, \u20139); \u201332% (\u201339, \u201323) and \u201337% (\u201346, \u201326), respectively]. In contrast, LSGM concentra- tions of monoisobutyl phthalate, mono(3-carboxypropyl) phthalate (MCPP), monocarboxyoctyl phthalate, and monocarboxynonyl phthalate (MCNP) increased over the study period [percent change (95% CI): 206% (178, 236); 25% (8, 45); 149% (102, 207); and 15% (1, 30), respectively]. Trends varied by subpopulations for certain phthalates. For example, LSGM concentrations of \u2211DEHP metabolites, MCPP, and MCNP were higher in children than adults, but the gap between groups narrowed over time (pinteraction < 0.01). CONCLUSIONS: Exposure of the U.S. population to phthalates has changed in the last decade. Data gaps make it difficult to explain trends, but legislative activity and advocacy campaigns by non- governmental organizations may play a role in changing trends.", "author" : [{ "dropping-particle" : "", "family" : "Zota", "given" : "Ami R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Calafat", "given" : "Antonia M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Woodruff", "given" : "Tracey J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "235-241", "title" : "Temporal trends in phthalate exposures: Findings from the national health and nutrition examination survey, 2001-2010", "type" : "article-journal", "volume" : "122" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cdb658c0-4cc9-4fc1-81ba-4ba695cab302"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1016/j.envint.2015.08.005", "ISBN" : "0324141122", "ISSN" : "1527-5418", "PMID" : "24655651", "author" : [{ "dropping-particle" : "", "family" : "Johns", "given" : "Lauren E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cooper", "given" : "Glinda S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Galizia", "given" : "Audrey", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Meeker", "given" : "John D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environment International", "id" : "ITEM-2", "issue" : "2", "issued" : { "date-parts" : [["2016"]] }, "page" : "137-143",

"title" : "Exposure Assessment Issues in Epidemiology Studies of Phthalates", "type" : "article-journal", "volume" : "150" }, "uris" : ["http://www.mendeley.com/documents/?uuid=85459219-e9ce-48b5-b13a-63641419edff"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1016/j.envres.2016.11.012", "ISSN" : "00139351", "author" : [{ "dropping-particle" : "", "family" : "Gyllenhammar", "given" : "Irina", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Glynn", "given" : "Anders", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "J\u00f6nsson", "given" : "Bo A.G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lindh", "given" : "Christian H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Darnerud", "given" : "Per Ola", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Svensson", "given" : "Kettil", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lignell", "given" : "Sanna", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Research", "id" : "ITEM-3", "issue" : "November 2016", "issued" : { "date-parts" : [["2017"]] }, "page" : "48-54", "publisher" : "Elsevier", "title" : "Diverging temporal trends of human exposure to bisphenols and plastizisers, such as phthalates, caused by substitution of legacy EDCs?", "type" : "article-journal", "volume" : "153" }, "uris" : ["http://www.mendeley.com/documents/?uuid=325eff1a-aa6a-4b43-b3cc-d4da1f3562f0"] }], "mendeley" : { "formattedCitation" : "(Gyllenhammar et al. 2017; Johns et al. 2016; Zota et al. 2014)", "plainTextFormattedCitation" : "(Gyllenhammar et al. 2017; Johns et al. 2016; Zota et al. 2014)", "previouslyFormattedCitation" : "(Gyllenhammar et al. 2017; Johns et al. 2016; Zota et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. We did agree with Qian et al.'s finding that coexposures among the six phthalates changed as a function of daily intake. Those participants at the upper ends of exposure (as quantified by the daily intake dose) were primarily driven by one phthalate and for the 2007-2008 NHANES cycle, while coexposure patterns remained fairly consistent when presented by age, ethnicity, and gender. This negative correlation has been seen in a number of other studies of risk ranging from cumulative exposures to mixtures of chemicals in water and indoor air (Price et al. 2011, Han et al. 2011, De Brouwere et al. 2014, Silvia and Cerejeira 2015, Vallotton and Price, 2016). Our work confirmed this pattern by demonstrating a robust negative correlation between MCR and HI.

This cycle of the NHANES data did not include phthalate metabolites from children under the age of six. This may be particularly problematic due to hand-to-mouth and object-to-mouth behavior especially with children's toys that may contain phthalates [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "doi.org/10.1016/j.cppeds.2007.11.001", "author" : [{ "dropping-particle" : "", "family" : "Sathyanarayana", "given" : "Sheela", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Current Problems in Pediatric and Adolescent Health Care", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2008"]] }, "page" : "34-49", "title" : "Phthalates and Children\u2019s Health", "type" : "article-journal", "volume" : "38" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0bf47f51-307f-4f53-b667-be4526a06fdf"] }], "mendeley" : { "formattedCitation" : "(Sathyanarayana 2008)", "plainTextFormattedCitation" : "(Sathyanarayana 2008)", "previouslyFormattedCitation" : "(Sathyanarayana 2008)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. If infants and small children had sources of exposure that differ from the older children in this study, then these findings may not be relevant to that age group. NHANES is also a national survey. Thus, small local populations with unique exposure sources may not be reflected. Exposure patterns for phthalates can differ between geopolitical regions [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1021/es504455a", "ISBN" : "ISSN 0013-936X", "ISSN" : "15205851", "PMID" : "25496010", "abstract" : "We analyzed 13 metabolites of 9 phthalates in urine of

782 Chinese school children aged 8-11 years and estimated the daily intake for phthalates based on urinary metabolite levels. The daily intakes were compared with acceptable intake levels to calculate the hazard quotient (HQ) for single phthalate. Finally, the cumulative risk for each child was assessed by means of a hazard index (HI) which is the sum of HQs. Overall, 11 metabolites were found in at least 85% of the urine samples with the highest median concentration of 47.1 ng/mL (93.4 \u03bcg/g creatinine) for mono-n-butyl phthalate (MnBP). Monooctyl phthalate (MOP) and monoisononyl phthalate (MiNP) were not detectable. The cumulative risk assessment covering di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DnBP), di-isobutyl phthalate (DiBP), and butyl-benzyl phthalate (BBzP) demonstrated that 19.8% (volume model-based) and 40.3% (creatinine model-based) of the children exceeded 1 for the HI based on tolerable daily intake (TDI) values (considered as potential adverse antiandrogenic effect). Furthermore, at least 36% of the children from the manufacturing-intensive region had a HI higher than 1. The results indicate that Chinese children are widely exposed to phthalates and those from manufacturing-intensive regions are probably at a high risk of cumulative phthalate exposure.", "author" : [{ "dropping-particle" : "", "family" : "Wang", "given" : "Bin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wang", "given" : "Hexing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wei", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Yue", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Ying", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Qingwu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Science and Technology", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2015"]] }, "page" : "1120-1129", "title" : "Urinary excretion of phthalate metabolites in school children of China: Implication for cumulative risk assessment of phthalate exposure", "type" : "article-journal", "volume" : "49" }, "uris" : ["http://www.mendeley.com/documents/?uuid=437d2826-57f4-4e60-9570-51346f28e783"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1016/j.envres.2016.07.025", "ISSN" : "10960953", "PMID" : "27466754", "abstract" : "Phthalate esters (PEs) and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) used as additives in numerous consumer products are continuously released into the environment, leading to subsequent human exposure which might cause adverse health effects. The human biomonitoring approach allows the detection of PEs and DINCH in specific populations, by taking into account all possible routes of exposure (e.g. inhalation, transdermal and oral) and all relevant sources (e.g. air, dust, personal care products, diet). We have investigated the presence of nine PE and two DINCH metabolites and their exposure determinants in 61 adult residents of the Oslo area (Norway). Three urine spots and fingernails were collected from each participant according to established sampling protocols. Metabolite analysis was performed by LC-MS/MS. Metabolite levels in urine were used to back-calculate the total exposure to their corresponding parent compound. The primary monoesters, such as monomethyl phthalate (MMP, geometric mean 89.7??ng/g), monoethyl phthalate (MEP, 104.8??ng/g) and mono-n-butyl phthalate (MnBP, 89.3??ng/g) were observed in higher levels in nails, whereas the secondary bis(2-ethylhexyl) phthalate (DEHP) and DINCH oxidative metabolites were more abundant in urine (detection frequency 84???100%). The estimated daily intakes of PEs and DINCH for this Norwegian population did not exceed the established tolerable daily intake and reference doses, and the cumulative risk assessment for combined exposure to plasticizers with similar toxic endpoints indicated no health concerns for the selected population. We found a moderate positive correlation between MEP levels in 3 urine spots and nails (range: 0.56???0.68). Higher frequency of personal care products use was associated with greater MEP concentrations in both urine and nail samples. Increased age, smoking, wearing plastic gloves during house cleaning, consuming food with plastic packaging and eating with hands were associated with higher levels in urine and nails for some of the metabolites. In contrast, frequent hair and hand washing was associated with lower urinary

levels of monoisobutyl phthalate (MiBP) and mono(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), respectively.", "author" : [{ "dropping-particle" : "", "family" : "Giovanoulis", "given" : "Georgios", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Alves", "given" : "Andreia", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Papadopoulou", "given" : "Eleni", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cousins", "given" : "Anna Palm", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sch\u00fctze", "given" : "Andr\u00e9", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Koch", "given" : "Holger M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Haug", "given" : "Line S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Covaci", "given" : "Adrian", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Magn\u00e9r", "given" : "J\u00f6rgen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Voorspoels", "given" : "Stefan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Research", "id" : "ITEM-2", "issued" : { "date-parts" : [["2016"]] }, "page" : "80-90", "publisher" : "Elsevier", "title" : "Evaluation of exposure to phthalate esters and DINCH in urine and nails from a Norwegian study population", "type" : "article-journal", "volume" : "151" }, "uris" : ["http://www.mendeley.com/documents/?uuid=3b7080a8-5555-4988-8ad9-08f6979c1893"] }], "mendeley" : { "formattedCitation" : "(Giovanoulis et al. 2016; Wang et al. 2015)", "plainTextFormattedCitation" : "(Giovanoulis et al. 2016; Wang et al. 2015)", "previouslyFormattedCitation" : "(Giovanoulis et al. 2016; Wang et al. 2015)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }], thus these findings may not be appropriate for populations outside of the U.S.

The NHANES data are cross-sectional snapshots of metabolite concentrations. The use of cross sectional data to characterize exposures is known to introduce a bias in the measurement of interindividual variation in exposures due to the data reflecting both inter and intraindividual variation in metabolite concentrations [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1080/15287394.2013.821394", "ISBN" : "1528-7394", "ISSN" : "ISSN 1528-7394 EISSN 1087-2620", "PMID" : "23980840", "abstract" : "Human biomarker measurements in tissues including blood, breath, and urine can serve as efficient surrogates for environmental monitoring because a single biological sample integrates personal exposure across all environmental media and uptake pathways. However, biomarkers represent a snapshot in time, and risk assessment is generally based on long-term averages. In this study, a statistical approach is proposed for estimating long-term average exposures from distributions of spot biomarker measurements using intraclass correlations based upon measurement variance components from the literature. This methodology was developed and demonstrated using a log-normally distributed data set of urinary OH-pyrene taken from our own studies. The calculations are generalized for any biomarker data set of spot measures such as those from the National Health and Nutrition Evaluation Studies (NHANES) requiring only spreadsheet calculations. A three-tiered approach depending on the availability of metadata was developed for converting any collection of spot biomarkers into an estimated distribution of individual means that can then be compared to a biologically relevant risk level. Examples from a Microsoft Excel-based spreadsheet for calculating estimates of the proportion of the population exceeding a given biomonitoring equivalent level are provided as an appendix.", "author" : [{ "dropping-particle" : "", "family" : "Pleil", "given" : "J D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sobus", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Toxicology and Environmental Health, Part A: Current Issues", "id" : "ITEM-1", "issue" : "August", "issued" : { "date-parts" : [["2013"]] }, "page" : "747-766", "title" : "Estimating Lifetime Risk from Spot Biomarker Data and Intraclass Correlation Coefficients (ICC)", "type" : "article-journal",

"volume" : "76" }, "uris" : ["http://www.mendeley.com/documents/?uuid=588ae4a4-1a22-422f-92dd-e302a9e86283"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1289/ehp.1104139", "ISBN" : "1552-9924 (Electronic)\\r0091-6765 (Linking)", "ISSN" : "00916765", "PMID" : "22262702", "abstract" : "BACKGROUND Gestational phthalate and bisphenol A (BPA) exposure may increase the risk of adverse maternal/child health outcomes, but there are few data on the variability of urinary biomarkers before and during pregnancy. OBJECTIVE We characterized the variability of urinary phthalate metabolite and BPA concentrations before and during pregnancy and the ability of a single spot urine sample to classify average gestational exposure. METHODS We collected 1,001 urine samples before and during pregnancy from 137 women who were partners in couples attending a Boston fertility clinic and who had a live birth. Women provided spot urine samples before (n \u2265 2) and during (n \u2265 2) pregnancy. We measured urinary concentrations of monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-iso-butyl phthalate, monobenzyl phthalate (MBzP), four metabolites of di-(2-ethylhexyl) phthalate (DEHP), and BPA. After adjusting for specific gravity, we characterized biomarker variability using intraclass correlation coefficients (ICCs) and conducted several surrogate category analyses to determine whether a single spot urine sample could adequately classify average gestational exposure. RESULTS Absolute concentrations of phthalate metabolites and BPA were similar before and during pregnancy. Variability was higher during pregnancy than before pregnancy for BPA and MBzP, but similar during and before pregnancy for MBP, MEP, and \u03a3DEHP. During pregnancy, MEP (ICC = 0.50) and MBP (ICC = 0.45) were less variable than BPA (ICC = 0.12), MBzP (ICC = 0.25), and \u03a3DEHP metabolites (ICC = 0.08). Surrogate analyses suggested that a single spot urine sample may reasonably classify MEP and MBP concentrations during pregnancy, but more than one sample may be necessary for MBzP, DEHP, and BPA. CONCLUSIONS Urinary phthalate metabolites and BPA concentrations were variable before and during pregnancy, but the magnitude of variability was biomarker specific. A single spot urine sample adequately classified MBP and MEP concentrations during pregnancy. The present results may be related to unique features of the women studied, and replication in other pregnancy cohorts is recommended.", "author" : [{ "dropping-particle" : "", "family" : "Braun", "given" : "Joe M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Smith", "given" : "Kristen W.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Williams", "given" : "Paige L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Calafat", "given" : "Antonia M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berry", "given" : "Katharine", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ehrlich", "given" : "Shelley", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hauser", "given" : "Russ", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-2", "issue" : "5", "issued" : { "date-parts" : [["2012"]] }, "page" : "739-745", "title" : "Variability of urinary phthalate metabolite and bisphenol a concentrations before and during pregnancy", "type" : "article-journal", "volume" : "120" }, "uris" : ["http://www.mendeley.com/documents/?uuid=85286677-dd9a-45be-a40d-8d63a2ae8b70"] }], "mendeley" : { "formattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)", "plainTextFormattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)", "previouslyFormattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Intraindividual variation is larger for rapidly cleared compounds than persistent compounds. The phthalates and their metabolites are typically fully excreted in the urine or feces within one to two days [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1098/rstb.2008.0208", "ISBN" : "1471-2970 (Electronic)\\r0962-8436 (Linking)", "ISSN" : "1471-2970", "PMID" : "19528056", "abstract" : "In the last decades, the availability of sophisticated analytical chemistry techniques has facilitated measuring trace levels of multiple environmental chemicals in

human biological matrices (i.e. biomonitoring) with a high degree of accuracy and precision. As biomonitoring data have become readily available, interest in their interpretation has increased. We present an overview on the use of biomonitoring in exposure and risk assessment using phthalates and bisphenol A as examples of chemicals used in the manufacture of plastic goods. We present and review the most relevant research on biomarkers of exposure for phthalates and bisphenol A, including novel and most comprehensive biomonitoring data from Germany and the United States. We discuss several factors relevant for interpreting and understanding biomonitoring data, including selection of both biomarkers of exposure and human matrices, and toxicokinetic information.", "author" : [{ "dropping-particle" : "", "family" : "Koch", "given" : "Holger M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Calafat", "given" : "Antonia M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Philosophical transactions of the Royal Society", "id" : "ITEM-1", "issue" : "1526", "issued" : { "date-parts" : [["2009"]] }, "page" : "2063-78", "title" : "Human body burdens of chemicals used in plastic manufacture", "type" : "article-journal", "volume" : "364" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8dfb7f2f-e157-44dd-a807-183efbd6f9ee"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1016/j.envint.2014.07.011", "ISBN" : "0160-4120", "ISSN" : "18736750", "PMID" : "25137624", "abstract" : "The quality of exposure assessment is a major determinant of the overall quality of any environmental epidemiology study. The use of biomonitoring as a tool for assessing exposure to ubiquitous chemicals with short physiologic half-lives began relatively recently. These chemicals present several challenges, including their presence in analytical laboratories and sampling equipment, difficulty in establishing temporal order in cross-sectional studies, short- and long-term variability in exposures and biomarker concentrations, and a paucity of information on the number of measurements required for proper exposure classification. To date, the scientific community has not developed a set of systematic guidelines for designing, implementing and interpreting studies of short-lived chemicals that use biomonitoring as the exposure metric or for evaluating the quality of this type of research for WOE assessments or for peer review of grants or publications. We describe key issues that affect epidemiology studies using biomonitoring data on short-lived chemicals and propose a systematic instrument - the Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument - for evaluating the quality of research proposals and studies that incorporate biomonitoring data on short-lived chemicals. Quality criteria for three areas considered fundamental to the evaluation of epidemiology studies that include biological measurements of short-lived chemicals are described: 1) biomarker selection and measurement, 2) study design and execution, and 3) general epidemiological study design considerations. We recognize that the development of an evaluative tool such as BEES-C is neither simple nor non-controversial. We hope and anticipate that the instrument will initiate further discussion/debate on this topic. ?? 2014 The Authors.", "author" : [{ "dropping-particle" : "", "family" : "LaKind", "given" : "Judy S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sobus", "given" : "Jon R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Goodman", "given" : "Michael", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Barr", "given" : "Dana Boyd", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "F\u00fcrst", "given" : "Peter", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Albertini", "given" : "Richard J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arbuckle", "given" : "Tye E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schoeters", "given" : "Greet", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tan", "given" : "Yu Mei", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Teeguarden", "given" : "Justin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tornero-Velez", "given" : "Rogelio", "non-

dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Weisel", "given" : "Clifford P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environment International", "id" : "ITEM-2", "issued" : { "date-parts" : [["2014"]] }, "page" : "195-207", "publisher" : "The Authors", "title" : "A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument", "type" : "article-journal", "volume" : "73" }, "uris" : ["http://www.mendeley.com/documents/?uuid=4360263c-26d4-4991-a819-839ce77482fc"] }], "mendeley" : { "formattedCitation" : "(Koch and Calafat 2009; LaKind et al. 2014)", "plainTextFormattedCitation" : "(Koch and Calafat 2009; LaKind et al. 2014)", "previouslyFormattedCitation" : "(Koch and Calafat 2009; LaKind et al. 2014)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. The steady state assumption may overestimate the size of the doses received in participants with larger internal doses [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1080/15287394.2013.821394", "ISBN" : "1528-7394", "ISSN" : "ISSN 1528-7394 EISSN 1087-2620", "PMID" : "23980840", "abstract" : "Human biomarker measurements in tissues including blood, breath, and urine can serve as efficient surrogates for environmental monitoring because a single biological sample integrates personal exposure across all environmental media and uptake pathways. However, biomarkers represent a snapshot in time, and risk assessment is generally based on long-term averages. In this study, a statistical approach is proposed for estimating long-term average exposures from distributions of spot biomarker measurements using intraclass correlations based upon measurement variance components from the literature. This methodology was developed and demonstrated using a log-normally distributed data set of urinary OH-pyrene taken from our own studies. The calculations are generalized for any biomarker data set of spot measures such as those from the National Health and Nutrition Evaluation Studies (NHANES) requiring only spreadsheet calculations. A three-tiered approach depending on the availability of metadata was developed for converting any collection of spot biomarkers into an estimated distribution of individual means that can then be compared to a biologically relevant risk level. Examples from a Microsoft Excel-based spreadsheet for calculating estimates of the proportion of the population exceeding a given biomonitoring equivalent level are provided as an appendix.", "author" : [{ "dropping-particle" : "", "family" : "Pleil", "given" : "J D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sobus", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Toxicology and Environmental Health, Part A: Current Issues", "id" : "ITEM-1", "issue" : "August", "issued" : { "date-parts" : [["2013"]] }, "page" : "747-766", "title" : "Estimating Lifetime Risk from Spot Biomarker Data and Intraclass Correlation Coefficients (ICC)", "type" : "article-journal", "volume" : "76" }, "uris" : ["http://www.mendeley.com/documents/?uuid=588ae4a4-1a22-422f-92dd-e302a9e86283"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1289/ehp.1104139", "ISBN" : "1552-9924 (Electronic)\\r0091-6765 (Linking)", "ISSN" : "00916765", "PMID" : "22262702", "abstract" : "BACKGROUND Gestational phthalate and bisphenol A (BPA) exposure may increase the risk of adverse maternal/child health outcomes, but there are few data on the variability of urinary biomarkers before and during pregnancy. OBJECTIVE We characterized the variability of urinary phthalate metabolite and BPA concentrations before and during pregnancy and the ability of a single spot urine sample to classify average gestational exposure. METHODS We collected 1,001 urine samples before and during pregnancy from 137 women who were partners in couples attending a Boston fertility clinic and who had a live birth. Women provided spot urine samples before (n \u2265 2) and during (n \u2265 2) pregnancy. We measured urinary concentrations of monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-iso-butyl phthalate, monobenzyl phthalate (MBzP), four metabolites of di-(2-ethylhexyl) phthalate (DEHP), and BPA. After adjusting for specific gravity, we characterized biomarker variability using intraclass correlation coefficients (ICCs) and conducted several surrogate category analyses to determine whether a single spot urine sample could adequately classify average gestational exposure. RESULTS

Absolute concentrations of phthalate metabolites and BPA were similar before and during pregnancy. Variability was higher during pregnancy than before pregnancy for BPA and MBzP, but similar during and before pregnancy for MBP, MEP, and \u03a3DEHP. During pregnancy, MEP (ICC = 0.50) and MBP (ICC = 0.45) were less variable than BPA (ICC = 0.12), MBzP (ICC = 0.25), and \u03a3DEHP metabolites (ICC = 0.08). Surrogate analyses suggested that a single spot urine sample may reasonably classify MEP and MBP concentrations during pregnancy, but more than one sample may be necessary for MBzP, DEHP, and BPA. CONCLUSIONS Urinary phthalate metabolites and BPA concentrations were variable before and during pregnancy, but the magnitude of variability was biomarker specific. A single spot urine sample adequately classified MBP and MEP concentrations during pregnancy. The present results may be related to unique features of the women studied, and replication in other pregnancy cohorts is recommended.", "author" : [{ "dropping-particle" : "", "family" : "Braun", "given" : "Joe M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Smith", "given" : "Kristen W.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Williams", "given" : "Paige L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Calafat", "given" : "Antonia M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berry", "given" : "Katharine", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ehrlich", "given" : "Shelley", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hauser", "given" : "Russ", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Health Perspectives", "id" : "ITEM-2", "issue" : "5", "issued" : { "date-parts" : [["2012"]] }, "page" : "739-745", "title" : "Variability of urinary phthalate metabolite and bisphenol a concentrations before and during pregnancy", "type" : "article-journal", "volume" : "120" }, "uris" : ["http://www.mendeley.com/documents/?uuid=85286677-dd9a-45be-a40d-8d63a2ae8b70"] }], "mendeley" : { "formattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)", "plainTextFormattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)", "previouslyFormattedCitation" : "(Braun et al. 2012; Pleil and Sobus 2013)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. We have not attempted to correct the predictions of interindividual variation in the DI for this effect, however, we acknowledge that measures of the percentages of the upper and lower tails of the distributions are likely to be overestimated. While this was of little concern for the lower tail, it was an important issue for the evaluation of the doses predicted for the upper tails of the population. As a result, the true fraction of the population with $HI > 1$ is likely to be lower than the values presented here.

This work assumed that there was a one-to-one correspondence between the metabolites and the phthalates from which they originate and each metabolite can be used to determine the dose of the parent compound based on a measured fraction of a chemical excreted as a specific metabolite (F_{UE}). For the metabolites originating from DIBP, DBP, and BBP the value of F_{UE} was 70% or greater. However, for the metabolites originating from DINP and DIDP, the values were less 10%. This difference introduces a larger uncertainty in the predictions of DI for these compounds. Finally, the values of HQ, HI, and MCR for the surveyed participants were dependent of the choice of the toxicity values. Toxicity values used here were based on common endpoints [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.reprotox.2010.04.005", "author" : [{ "dropping-particle" : "", "family" : "Christiansen", "given" : "Sofie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Boberg", "given" : "Julie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Axelstad", "given" : "Marta", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dalgaard", "given" : "Majken", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vinggaard", "given" : "Anne Marie", "non-dropping-particle" : "",

"parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Metzdorff", "given" : "Stine Broeng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hass", "given" : "Ulla", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Reproductive Toxicology", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2010"]] }, "page" : "313-321", "title" : "Low-dose perinatal exposure to di(2-ethylhexyl) phthalate induces anti-androgenic effects in male rats", "type" : "article-journal", "volume" : "30" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e49a8825-c15e-4d46-a4dd-afad7e772998"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1021/es504455a", "ISBN" : "ISSN 0013-936X", "ISSN" : "15205851", "PMID" : "25496010", "abstract" : "We analyzed 13 metabolites of 9 phthalates in urine of 782 Chinese school children aged 8-11 years and estimated the daily intake for phthalates based on urinary metabolite levels. The daily intakes were compared with acceptable intake levels to calculate the hazard quotient (HQ) for single phthalate. Finally, the cumulative risk for each child was assessed by means of a hazard index (HI) which is the sum of HQs. Overall, 11 metabolites were found in at least 85% of the urine samples with the highest median concentration of 47.1 ng/mL (93.4 \u03bcg/g creatinine) for mono-n-butyl phthalate (MnBP). Monooctyl phthalate (MOP) and monoisononyl phthalate (MiNP) were not detectable. The cumulative risk assessment covering di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DnBP), di-isobutyl phthalate (DiBP), and butyl-benzyl phthalate (BBzP) demonstrated that 19.8% (volume model-based) and 40.3% (creatinine model-based) of the children exceeded 1 for the HI based on tolerable daily intake (TDI) values (considered as potential adverse antiandrogenic effect). Furthermore, at least 36% of the children from the manufacturing-intensive region had a HI higher than 1. The results indicate that Chinese children are widely exposed to phthalates and those from manufacturing-intensive regions are probably at a high risk of cumulative phthalate exposure.", "author" : [{ "dropping-particle" : "", "family" : "Wang", "given" : "Bin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wang", "given" : "Hexing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wei", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Yue", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Ying", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Qingwu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Science and Technology", "id" : "ITEM-2", "issue" : "2", "issued" : { "date-parts" : [["2015"]] }, "page" : "1120-1129", "title" : "Urinary excretion of phthalate metabolites in school children of China: Implication for cumulative risk assessment of phthalate exposure", "type" : "article-journal", "volume" : "49" }, "uris" : ["http://www.mendeley.com/documents/?uuid=437d2826-57f4-4e60-9570-51346f28e783"] }], "mendeley" : { "formattedCitation" : "(Christiansen et al. 2010; Wang et al. 2015)", "plainTextFormattedCitation" : "(Christiansen et al. 2010; Wang et al. 2015)", "previouslyFormattedCitation" : "(Christiansen et al. 2010; Wang et al. 2015)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }].

Because the data suggested that the cumulative exposures to the typical individual were of relatively low concern (i.e. HI values in the surveyed participants averaged 0.15), future work should include investigation into the sources of DEHP, DINP, and DIDP that drive high levels of exposure in small portions of the general population. This could work could include investigating functional use and production of these three phthalates. The investigation should also seek to determine if there are overlaps between the populations with high exposures of the three compounds.

Data from previous NHANES cycles can be incorporated to investigate population-wide temporal trends in hazards of phthalates across the years. Mitigation and substitution strategies of phthalates can change over time [ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" :

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and reference doses, and the cumulative risk assessment for combined exposure to plasticizers with similar toxic endpoints indicated no health concerns for the selected population. We found a moderate positive correlation between MEP levels in 3 urine spots and nails (range: 0.56???0.68). Higher frequency of personal care products use was associated with greater MEP concentrations in both urine and nail samples. Increased age, smoking, wearing plastic gloves during house cleaning, consuming food with plastic packaging and eating with hands were associated with higher levels in urine and nails for some of the metabolites. In contrast, frequent hair and hand washing was associated with lower urinary levels of monoisobutyl phthalate (MiBP) and mono(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), respectively.", "author" : [{ "dropping-particle" : "", "family" : "Giovanoulis", "given" : "Georgios", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Alves", "given" : "Andreia", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Papadopoulou", "given" : "Eleni", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cousins", "given" : "Anna Palm", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sch\u00fctze", "given" : "Andr\u00e9", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Koch", "given" : "Holger M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Haug", "given" : "Line S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Covaci", "given" : "Adrian", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Magn\u00e9r", "given" : "J\u00f6rgen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Voorspoels", "given" : "Stefan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Environmental Research", "id" : "ITEM-2", "issued" : { "date-parts" : [["2016"]] }, "page" : "80-90", "publisher" : "Elsevier", "title" : "Evaluation of exposure to phthalate esters and DINCH in urine and nails from a Norwegian study population", "type" : "article-journal", "volume" : "151" }, "uris" : ["http://www.mendeley.com/documents/?uuid=3b7080a8-5555-4988-8ad9-08f6979c1893"] }], "mendeley" : { "formattedCitation" : "(Bui et al. 2016; Giovanoulis et al. 2016)", "plainTextFormattedCitation" : "(Bui et al. 2016; Giovanoulis et al. 2016)", "previouslyFormattedCitation" : "(Bui et al. 2016; Giovanoulis et al. 2016)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]. Thus, ongoing monitoring and analyses are appropriate going forward. Finally, the absence of biomontoring data in children under the age of six suggests the need for new strategies for characterizing aggregate phthalate exposures to infants and small children.

CONCLUSIONS

This was the first work to visualize the MCR and HI measures on a log-log scale and the second work to apply the MCR metric to biomonitoring data. We found that the majority of participants with HI values around the 99th percentile could be identified by a chemical-by-chemical assessment. An $HI > 1$ from the six phthalates only occurred in a small fraction of the population (0.8%). Elevated risks (i.e. participants with $HI > 1$) were generally not associated with cumulative exposures but were largely due to high levels of one of two phthalates. Approximately 43% of subjects analyzed would not be considered to be at-risk if only the HQs for the six individual phthalates were investigated. We conclude that performing a cumulative assessment had a measurable but modest impact in the evaluation of hazards among six phthalates in individuals aged six years and older.

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Table 1. Data on Tolerable daily intakes, metabolites, and metabolites detection limits from the 2013-2014 NHANES cycle.

Phthalate (Parent)	Tolerable Daily Intakes (ug/kg/d)	Metabolite	Limit of Detection in NHANES (ng/mL)	Number of samples below the Limit of Detection (%)
di-n-butyl phthalate (DBP)[a]	10	monobutyl phthalate (MBP)	0.4	43 (1.6)
diisobutyl phthalate (DIBP)[b]	1250	monoisobutyl phthalate (MIBP)	0.8	72 (2.7)
butyl benzyl phthalate (BBP)[c]	500	monobenzyl phthalate (MBZP)	0.3	63 (2.4)
di(2-ethylhexyl) phthalate (DEHP)[d]	50	mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)	0.4	6 (0.2)
		mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)	0.2	13 (0.5)
		mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	0.4	9 (0.3)
		mono(2-ethylhexyl) phthalate (MEHP)	0.8	1003 (37.66)
diisononyl phthalate (DINP)[e]	150	monoisononyl phthalate (MINP)	0.9	1586 (59.56)
		mono(carboxyoctyl) phthalate (MCOP)	0.3	3 (0.1)
diisodecyl phthalate (DIDP)[f]	130	mono(carboxynonyl) phthalate (MCNP)	0.2	32 (1.2)

[a][ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.2903/j.efsa.2004.84", "ISSN" : "1831-4732", "abstract" : "SUMMARY\\r\\nThe Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Foods (AFC Panel) has been asked to advise on the safety and bioavailability of ferrous bisglycinate when used as a source of iron in foods.\\r\\nIn 2004, The Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) evaluated the safety of iron in general, when present in fortified foods and food supplements, but considered that the available data were insufficient to establish a tolerable upper intake level for iron. The NDA Panel also indicated there are certain subgroups of the population (men and postmenopausal women) that may develop biochemical indicators of high iron stores by the additional intake of iron from food supplements. Based on estimates of current iron intakes in European countries, the NDA Panel concluded that the risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis.\\r\\nThe present opinion deals only with the safety and bioavailability of a particular source of iron, ferrous bisglycinate, intended for the general population, to be used in food supplements and in foods for particular nutritional uses. In addition, special attention has been paid to the use of ferrous bisglycinate as a source of iron in foods intended for infants and young children. The safety of iron itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.\\r\\nFerrous bisglycinate consists of one molecule of ferrous iron bound to two molecules of glycine to form two heterocyclic rings. For food fortification and dietary supplementation, ferrous bisglycinate is formulated containing 77% ferrous bisglycinate and food-grade citric acid (17%), maltodextrin (2%), silicon dioxide (0.01%), and water (4%).\\r\\nStudies to address the bioavailability and safety of ferrous bisglycinate have been conducted with ferrous bisglycinate. The absorption of iron from ferrous bisglycinate is regulated through the same physiological mechanisms as other inorganic forms of iron. Following oral administration, ferrous bisglycinate

adds to the intestinal intraluminal pool of inorganic, non-haem iron and is absorbed intact into the mucosal cells of the intestine, and is subsequently hydrolysed into its iron and glycine components. The iron compo\u2026", "author" : [{ "dropping-particle" : "", "family" : "Anton", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Barlow", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Boskou", "given" : "D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Castle", "given" : "L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Crebelli", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "W. Dekant, K.-H. Engel, S. Forsythe, W. Grunow, M. Heinonen, J.-C. Larsen, C. Leclercq, W. Mennes, M.-R. Milana, I. Pratt, I. Rietjens, K. Svensson, P. Tobback", "given" : "F. Toldr\u00e1.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "EFSA Journal", "id" : "ITEM-1", "issued" : { "date-parts" : [["2006"]] }, "page" : "1-17", "title" : "Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to Di-Butylphthalate (DBP) for use in food contact materials", "type" : "article-journal", "volume" : "299" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9f1c4fcd-7067-4641-a0a3-c6f8f749ec5d"] }], "mendeley" : { "formattedCitation" : "(Anton et al. 2006)", "plainTextFormattedCitation" : "(Anton et al. 2006)", "previouslyFormattedCitation" : "(Anton et al. 2006)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }]; [b][ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.reprotox.2008.07.006", "ISBN" : "0890-6238 (Print)\\r0890-6238 (Linking)", "ISSN" : "08906238", "PMID" : "18706996", "abstract" : "Diisobutyl phthalate (DIBP) is the branched isomer of DBP; DBP side chains have a four-carbon backbone (C4), whereas DIBP has its four-carbon alkyl side chains rearranged into a three-carbon backbone (C3) with a methyl branch. Di-n-butyl phthalate (DBP), and several other ortho-phthalate esters with side-chain lengths of C4-C6, are known to disrupt the androgen-dependent sexual differentiation in the male rat. This study was performed to determine whether in utero exposure to DIBP would induce permanent and dose-responsive alterations of male reproductive development. Pregnant Sprague-Dawley rats were administered olive oil (vehicle control), DIBP or DBP, by gavage on gestation Days 12-21, at doses of 125, 250, 500, 625 mg DIBP/(kg day) and 500 mg DBP/(kg day). DIBP caused no overt maternal toxicity, nor reduced litter size. Male offspring displayed reduced neonatal anogenital distance (Postnatal day 1, PND) at 250 mg DIBP/(kg day) and higher doses, and dose-related retention of areolas/nipples (PND 12-14). Preputial separation (onset of puberty) was delayed in male offspring at 500 and 625 mg DIBP/(kg day). Hypospadias, cleft prepuce, and undescended testis were observed in males (11-12 or 16-17 weeks old) exposed in utero to 500 and 625 mg DIBP/(kg day). Histopathological lesions were also present in adult testes, mainly consisting in seminiferous tubule degeneration. Our results show that DIBP can cause severe and specific adverse effects on the male rat reproductive development, with a pattern similar to that of DBP. However, DIBP appeared slightly less potent than DBP in inducing malformations. \u00a9 2008 Elsevier Inc. All rights reserved.", "author" : [{ "dropping-particle" : "", "family" : "Saillenfait", "given" : "Anne Marie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sabat\u00e9", "given" : "Jean Philippe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gallissot", "given" : "Fr\u00e9d\u00e9ric", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Reproductive Toxicology", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2008"]] }, "page" : "107-115", "title" : "Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male

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Table 2. A count of the phthalate producing the HQ_M for all participants in the 2013-2014 cycle of NHANES by phthalate and Group.

	I	II	IIIA	IIIB	Total
BBP	0	0	0	0	0
DBP	0	958	0	1	959
DEHP	3	712	1	1	717
DIBP	0	0	0	0	0
DIDP	1	25	0	0	26
DINP	8	947	5	1	961
Total	12	2642	6	3	2663

Table 3. Number of pairs of phthalates that appear as one of the top two HQs in the 21 participants with $HI > 1$.

	DEHP	DINP	DIDP	DBP
DEHP		12	2	1
DINP	---		5	1
DIDP	---	---		0
DBP	---	---	---	

Table 4. Count, percentage, and HI of total participants and participants by age group.

	Count			Percent			Hazard Index		
Group	6-17	18+	Total	6-17	18+	Total	Mean	Min	Max
I	3	9	12	0.4	0.5	0.5	2.2	1.1	5.0
II	741	1901	2642	98.9	99.3	99.2	0.1	0.0	1.0
III	5	4	9	0.7	0.2	0.3	1.1	1.0	1.4
Total	749	1914	2663	100.0	100.0	100.0	0.2	0.0	5.0
I or III	8	13	21	1.1	0.7	0.8	1.7	1.0	5.0

FIGURE LEGENDS

Figure 1. Plot of log HI versus $\log(MCR - 1)$ (with HQ_M/HI) of six phthalates for 2,663 participants from the 2013-2014 NHANES cycle identified by the phthalate that produced the HQ_M. Regions corresponding to Groups I, II, IIIA and IIIB and linear regression between log HI with $\log(MCR - 1)$ with 95% confidence interval ($slope = -0.395$ and $intercept = -0.421$) are provided.

Figure 2. Percent contribution to HI as quantified by the HQ from each of the six phthalates for ten participants from the 50th percentile of HI and ten participants from the 99th percentile of HI.

FIGURE 1

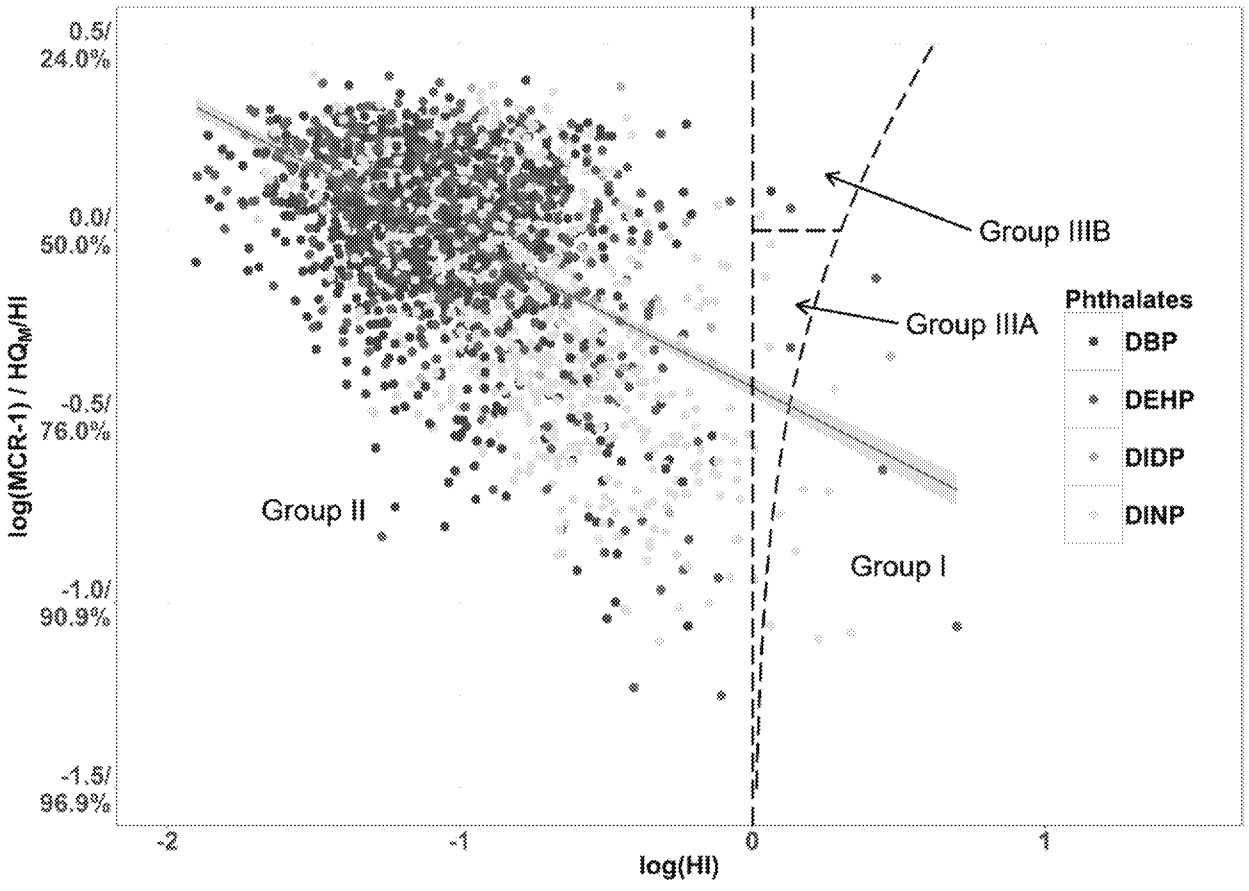
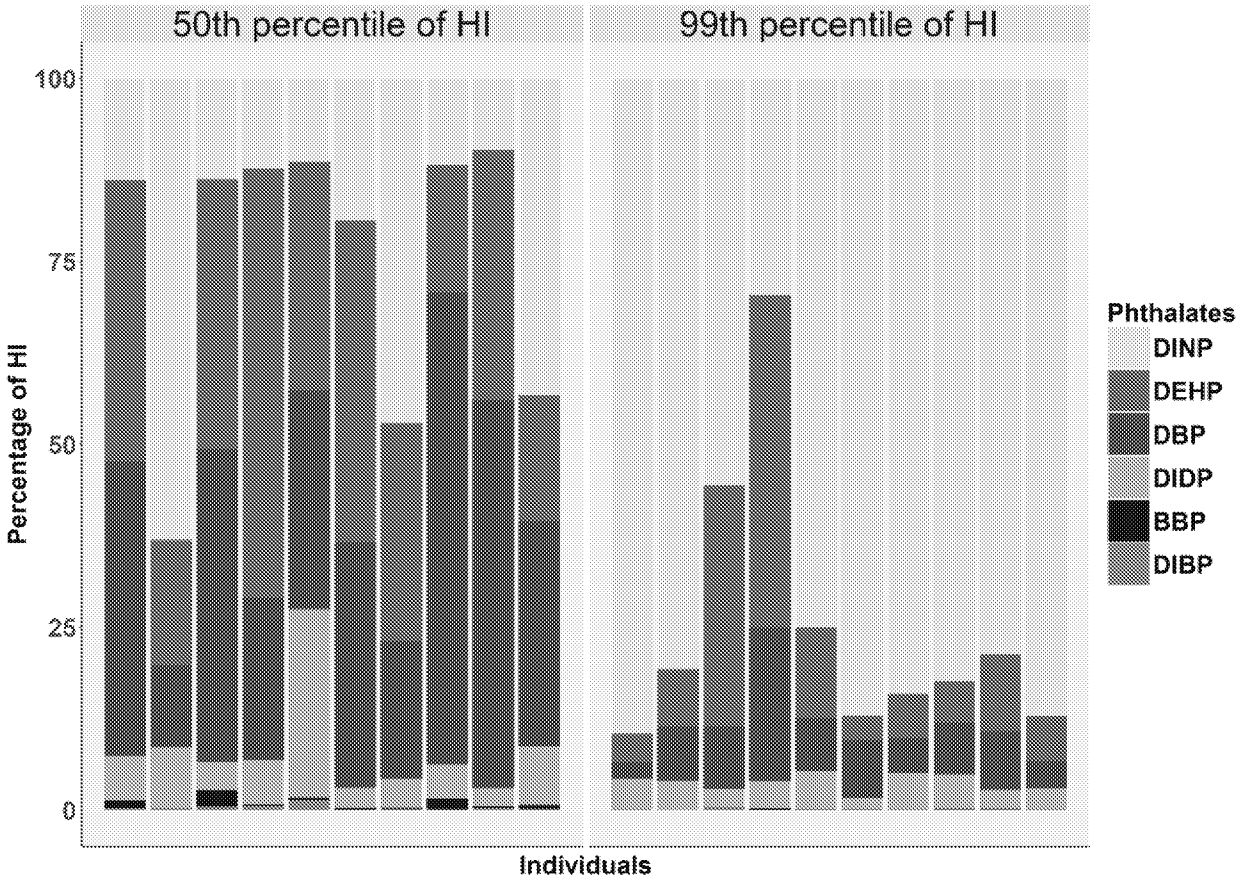

0.5/
24.0%
0.0/
50.0%
-0.5/
76.0%
-1.0/
90.9%
-1.5/
96.9%
log(MCR-1) / HQM/HI
-2
-1
0
1
log(HI)
Group IIIB
Group IIIA
Group II
Group I
Phthalates
DBP
DEHP
DIDP
DINP

FIGURE 2


50th percentile of HI
99th percentile of HI
100
75
50
25
0
Percentage of HI
Individuals
Phthalates
DINP
DEHP
DBP
DIDP
BBP
DIBP